CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-999

MEDICAL REVIEW

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 19 December 2006

FROM: Mitchell V. Mathis, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 21-999 (This overview should be filed with the 10-20-06 response submission.)

SUBJECT: Recommendation of Approval Action for Paliperidone Extended Release OROS Oral Tablets for the Treatment of Schizophrenia

1.0 PURPOSE

The purpose of this memo to file is to provide an interim update for NDA 21,999 since the Division issued an approvable letter to the sponsor dated 9/29/2006. The sponsor responded to this letter on 10/20/06. Please see the approvable memos from Drs. Khin and Laughren for a more detailed evaluation of the data that supported the original approvable action.

1.1 BACKGROUND

Paliperidone is a major active metabolite of risperidone which is an atypical antipsychotic agent approved in the treatment of schizophrenia. Both risperidone and paliperidone are centrally active dopamine D2 and 5-HT_{2A} antagonists. The proposed dose range in schizophrenia is 3 to 12 mg once daily.

2.0 CHEMISTRY

The chemists have identified no CMC concerns that would preclude an approval action on this NDA. CMC concerns about stability as listed in the approvable letter dated 9/29/2006 have been addressed and the data submitted support an [redacted] month initial expiry for the drug product.

3.0 PHARMACOLOGY

The pharmacologists have identified no pharmacology/toxicology issues that would preclude an approval action for this NDA.

4.0 CLINICAL PHARMACOLOGY

The clinical pharmacologists have not identified no areas of concern that would preclude an approval action for this NDA. Clinical Pharmacology and Biopharmaceutics found the originally proposed dissolution specifications unacceptable and proposed new specifications which have

been accepted by the sponsor. [redacted]

5.0 CLINICAL

5.1 Efficacy Data

Efficacy was determined from four 6-week, double-blind, randomized, parallel group, placebo-controlled trials in patients with acute exacerbations of schizophrenia. The primary endpoint was change from baseline in PANNS total score and the secondary endpoint was change from baseline in the Personal and Social Performance scale (PSP). Dosing was without regard to meals.

All doses in all 4 studies were statistically significantly superior to placebo on the PANSS. Paliperidone ER was also superior to placebo on PSP from these trials, and this is noted in labeling.

[redacted]

5.2 SAFETY

The safety data for this NDA were derived from a total of 2115 subjects/patients exposed to paliperidone ER across 37 clinical trials. Negotiations with the sponsor since the issuance of the approvable letter have focused on the potential for paliperidone ER to produce QT interval prolongation.

5.2.1 QT Prolongation

Although there is no signal from the phase 3 trials, paliperidone ER has a modest QT effect as judged from the sponsor's thorough QT study (SCH-1009). We consulted the Division of Cardiorenal Products (DCRP) for assistance in interpreting the results of this study and verification of corrected QT interval calculations from ECGs submitted to FDA's ECG warehouse. DCRP suggested language for the QT Prolongation section of labeling and recommended this language be included under Warnings because of the identified moderate risk (Pbo-subtracted QTcLD increase from baseline = 12.3 msec). We agree with this recommendation and have included this language under the Warnings section of labeling. The sponsor suggested that language describing [redacted]

5.2.2 Neonatal Effects

The sponsor had included labeling language under the Pregnancy which described the potential for extrapyramidal symptoms in the neonate. We consulted OND's Pregnancy Labeling Team (PLT) for their advice on this issue and recommendations for labeling. PLT provided general language describing the potential effects of maternal antipsychotic use on the neonate, and this language was accepted by the sponsor and incorporated into labeling.

5.0 PHASE 4 COMMITMENTS

Four phase 4 commitments were asked of the sponsor in the approvable letter of 9/29/2006. The sponsor has successfully argued that our initially-requested proton-pump inhibitor drug interaction study would not likely yield valuable information given that the OROS delivery system of the drug is not expected to be affected by gastric pH. The sponsor has agreed to the other three phase 4 commitments in the approvable letter. We should also include the deferred pediatric studies under PREA to be postmarketing study commitments.

6.0 LABELING AND ACTION LETTER

6.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed language has been modified. Our proposed labeling should be included in the action letter.

6.2.1 Foreign Labeling

At this time, I am not aware that paliperidone is approved for the treatment of schizophrenia anywhere.

7.0 CONCLUSIONS AND RECOMMENDATION

Sufficient data have been submitted to support the conclusion that paliperidone ER is effective and acceptably safe in the treatment of schizophrenia. We have identified three phase 4 commitments which were conveyed to the sponsor in the approvable letter dated 9/29/2006, and these continue to apply. I recommend that we approve this application.

Memorandum

To: File, NDA 21-999

From: Robert Temple, MD

Date: December 19, 2006

Subject: Approval of Paliperidone Extended Release Oros Oral Tablets for the treatment of schizophrenia

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Based on primary, secondary and tertiary reviews of safety and effectiveness, as well as reviews by chemistry, toxicology and clinical pharmacology, and DSI inspection, I agree that paliperidone has been shown to be effective in the acute treatment of schizophrenia. Maintenance treatment has not yet been studied. While the data stand on their own (3 placebo and active control dose-response studies and over 2000 patients in multiple dose trials), the fact that paliperidone is the principal active metabolite of risperidone means that there is an unusually large experience pertinent to this NME.

Doses from 3-15 mg per day were studied, with higher doses numerically somewhat better through 12 mg, but I agree with the recommended 6 mg (including elderly patients with normal renal function) starting dose and 12 mg maximum recommended dose, as well as elicitation of an agreement to explore lower doses further. There were only a few persuasively dose-related adverse events: akithesia, dystonia, extra-pyramidal disorder, somnolence, hypertonia, orthostatic hypotension, and salivary hypersecretion. Weight gains of $\geq$ 7% were increased in the 9 and 12 mg dose groups.

Despite the impression that risperidone had no material effect on QT, a relatively high dose of paliperidone IR showed a 12 msec effect. The concentrations expected with up to 12 mg ER should be lower, approximately those associated with a QT effect of about 6 msec. These data have led to a QT warning, but not to second line status, the risperidone experience is apparently benign. There were no patients in trials with QTc > 500 msec. The safety update review by Dr. Brugge did not describe any impressive prolongations.

I note late difficulties in agreeing on wording about the [redacted] and that the approved labeling will be silent on this. Most labeling for psychiatric drugs is silent on this point, so that I don't think the omission renders labeling false, but I believe this represents a needless loss of data. I note Dr. Mathis' discussion of this point and wonder whether we are over-refining our analyses. I start with knowing that the drug is effective, giving me a "prior" that it must work [redacted] This deserves further discussion, including good biometrics representation; the labeling can be promptly amended if we can agree on language.

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/s/

Robert Temple
12/19/2006 05:45:27 PM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies
Addendum to QT Study Review

NDA	21999
Brand Name	[redacted]
Generic Name	Paliperidone
Sponsor	Johnson & Johnson
Indication	Treatment of schizophrenia
Dosage Form	Oral
Therapeutic Dose	3-12 mg once daily
Duration of Therapeutic Use	Chronic Use
Review Classification	Standard
Clinical Division	Division of Psychiatry Products

1.0 GOAL OF THE REVIEW

This review serves as an addendum to a prior QT study review. The purpose of this review was to evaluate a subset of ECGs submitted to the ECG warehouse as part of study RO76477-SCH-1009

2.0 ECG ANALYSIS

A subset of at approximately 30-50 ECG tracings were reviewed to verify the Sponsor's QT measurements. This reviewer focused on those tracings with poor T-wave signal and low and high-frequency noise.

From this reviewer's perspective, the QT measurements appear to have been made appropriately.

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/s/

Shari Targum
12/1/2006 03:45:59 PM
MEDICAL OFFICER

Norman Stockbridge
12/1/2006 05:24:12 PM
MEDICAL OFFICER

Application Type	NDA 21-999 Response to an Approvable Letter
Submission Number Code	N0014
Letter Date	10/20/06
Received	10/20/06
PDUFA Goal Date	12/20/06
Reviewer Name	Karen Brugge, MD
Review Completion Date	11/17/06
Established Name	Paliperidone
(Proposed) Trade Name	[redacted]
Therapeutic Class	Atypical Antipsychotic
Applicant	Johnson & Johnson
Priority Designation	Standard
Formulation	Extended Release OROS® oral tablets
Indication	Schizophrenia
Intended Population	Adults with Schizophrenia

I. The Purpose of this Review and Background Information

The Purpose of This Review.

The purpose of this review is to assist the Team Leader and Director of the Division of Psychiatry Products in the regulatory processing of NDA [redacted]

Recommendations in this review are being provided from a clinical perspective. This NDA was given an Approvable Action as deemed by the Agency. This review focuses on the sponsor's responses to each Clinical item in the Approvable Letter that was deemed by the Agency as clinical issues that still need to be addressed before a final approval action may be granted. This review also focuses on labeling revisions of clinical sections of labeling that differ from labeling that was deemed by the Agency as acceptable labeling.

Other outstanding items that fall under other disciplines (as specified in the Approvable letter) and sections of labeling involving other disciplines are under review by the other disciplines (at the time of this writing). These are additional outstanding issues that need to be addressed before a final approvable action may be considered.

Each clinical item is copied from the Approvable Letter below (bolded text), followed by a summary of the sponsor's response. Note that the order of clinical issues, items E and F (F covers labeling) below is reversed from the order in which they appear in the Approvable letter, such that labeling may be addressed lastly in this review.

Background Information

The sponsor is seeking approval of Paliperidone OROS extended release tablets (Pal) for treatment of schizophrenia based on 3 positive 6-week Phase III trials conducted on patients with schizophrenia (that were generally in the acute episode). Refer to the original clinical review of NDA 21999 for details.

II. Clinical Items in the Approvable Action Letter and a Summary of the Sponsor's Responses

A. Clinical

Please submit the ECG data for study SCH-1009 to FDA's ECG warehouse so the QT measurements on these ECGs can be verified.

Summary of the Sponsor's Response
The sponsor provided the information as requested in the Action Letter and as requested by the QT team that was consulted regarding QT prolongation effects of Pal.

Reviewer Comment. *It is recommended that QT input be obtained on QT data submitted under the NDA, as the QT Team has requested.*

B. Foreign Regulatory Update/Labeling

We require a review of the status of all paliperidone actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If paliperidone has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for paliperidone along with English translations when needed.

Summary of the Sponsor's Response
Pal (ER tablet) is not approved in any country. "No negative action has been taken" with any of the sponsor's pending applications submitted to foreign countries (as listed in the submission, as of 10/2/06).

C. World Literature Update
Prior to the approval of paliperidone, we require an updated report on the world archival literature pertaining to the safety of paliperidone. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of paliperidone. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The NDA 21-999 Page 4 report should emphasize clinical data, but new findings in pre-clinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Summary of the Sponsor's Response
The sponsor summarized methodology of their updated search (for literature published between 4/1/06 and 7/31/06; note that 3/31/06 was the cut-off date used for literature search in the 210-SUR submission).

The following are listings of databases searched and search terms employed in the search, respectively (as copied from the submission)

Medline	Embase	Psych Info	Derwent Drug	Biosis
SciSearch	Chemical	Int Pharm Abs	File	Previews
Adis Clinical	Abstracts	ExtraMed	Life Sciences	Fedrip
Trials Insight	Conference		Collection	Pharmline
	Papers Index		JICST-Eplus	

The following primary search terms were included in the database search:

9-hydroxyrisperidone	9-hydroxy-risperidone	CAS Registry Number
9-OH-risperidone	paliperidone	144598-75.4

The sponsor explains that [redacted] conducted the search (assisted by J&JPRD Global Information Center) and that [redacted] reviewed the articles.

Only 3 out of 12 articles that were found in their search had safety data. According to the sponsor daily doses ranging from 3 mg to 15 mg were "safe in schizophrenia subjects up to 6 weeks."

Reviewer Comment.
Footnotes found in summaries of the above 3 articles (3 abstracts) provided in Attachment 1 of the submission indicated that the data in these abstracts "were extracted" from short-term Phase III trials -302, -303 and -305. Safety results from these trials were previously reviewed. Therefore, no new safety information could be found in the current submission.

The sponsor also provided results of updated reviews of the literature in previous NDA 21999 submissions; the 120-Day and 210-Day SUR submissions. This information was not previously reviewed as follows. The 210-SUR submission arrived late in the review cycle and was therefore not reviewed in the original and addendum clinical reviews of NDA 21999. Only clinical trial safety data provided in the 120-Day SUR was reviewed and summarized in the clinical review of NDA 2199. Consequently, the below subsection summarizes the results of the literature reviews described by the sponsor in these previous SUR submissions.

Summary of Literature Reviews in the 120-Day and 210-Day SUR submissions

The SURs used the same search terms and search databases as were employed for the current approvable response submission. A description of personnel that reviewed the search term results and articles could no be found in these previous submissions. Only a few publications with Pal were found which contained results from previously reviewed Phase III 6-week schizophrenia trials. Therefore, new information on Pal could not be found, that was not already described in the original review of NDA 21999. Risperidone studies that had safety information in reference to 9-OH-resperidone were summarized

and did not provide any new clinically remarkable safety observations that were not already described in the previous clinical reviews of NDA 21999. Several PK Risperidone-drug interaction studies were summarized that included results on PK properties of 9-OH-respiridone that the sponsor concluded did not provide any new information relevant to safety.

OCPB input is recommended regarding PK studies found in the sponsor's reviews of the literature that are included in the original and updated submissions under NDA 21999.

D. Safety Update

Our assessment of the safety of paliperidone is based on our review of all safety information provided in your original and subsequent submissions, including your safety update of December 31, 2005. Please provide a final serious events update to include serious adverse events up to a more recent cutoff date.

Reviewer Comment. *Newly submitted information summarized below does not change previously conveyed conclusions and recommendations provided in previous clinical reviews of NDA 21999.*

A Summary of the Sponsor's Response
The sponsor provides narratives for 5 subjects with newly reported SAEs since the reporting cut-off date for 210-Day SUR submission (these 5 SAEs that occurred between 3/31/06 and 8/31/06). The subjects are as follows: subjects 100323 and 100772 in Study R076477-SCH-701, subjects 500132, 500547, and 500655 in Study R076477-SCH-705.

Four of the 5 newly reported subjects with SAEs were SAEs of psychotic related events (e.g. schizophrenia) during OL treatment in which narrative descriptions did not describe any other unrelated events (e.g. potential drug effects on another organ system that may have lead to these psychiatric related events). The fifth subject (500547) was a 57 year old female patient (that appeared to be generally healthy) and was not receiving any concomitant medications. She developed dyspnea on Day 327 of OL treatment that was evaluated in the emergency room. This event was believed to be due to anxiety (ECG and "other unspecified tests...failed to show any organic findings..."). Therefore the subject was treated with diazepam for 5 days and the event resolved during the emergency room visit. Study medication was discontinued by the investigator on Day 338 (one day after a study visit during which no abnormalities on physical examination, ECG or vital signs were reported).

Reviewer Comment. *The reason why study medication was stopped in subject 50047 cannot be found in the narrative. Perhaps, cessation of treatment was related to lack of efficacy but this is only speculation on the part of the undersigned reviewer.*

Update on a Sudden Death during OL Treatment of 12 mg daily of Pal (Study -70)
The sponsor also provided updated information on a 23 year old female subject (100963 or [redacted] on the CIOMS form) with an unremarkable past medical history who died within hours after she became "breathless, anxious and agitated." This subject was given 2 mg trihexyphenidyl by her mother after developing these symptoms, "as per instruction" (2 mg BID was prescribed for extrapyramidal side effects of "masked facies"). She subsequently had "convulsions" and "loss of consciousness" for unclear reasons and died hours later after being seen in an emergency room, while she was being transported to another hospital. Refer to the clinical review and addendum clinical review of NDA 21999 for more details regarding this subject.

It appears that the new information being provided is the following:

- *The sponsor now reports that the investigator has more recently changed the terms used for the cause of death from "convulsion, bronchospasm, and respiratory failure" (as specified in the 210-Say SUR) to "convulsion" and "pulmonary embolism" (as specified in the current response to the Approvable letter submission and as found in a recent safety alert update report submitted under the IND). The SAE terms (and terms used for the cause of death) for this subject are now convulsion and pulmonary embolism since the investigator more recently suspected pulmonary embolism on the basis of the previously reported symptoms of breathlessness, anxiety and agitation that were described in past submissions as preceding the convulsion and loss of consciousness.*

Note that in the sponsor's proposed labeling (discussed later in this review), "bronchospasm" does not appear in the "Other Events Observed During the Premarketing..." section of labeling, while pulmonary embolism is now listed in this section.

No other new information from that previously described in the past clinical reviews of NDA 21999 can be found in the current updated description and narrative provided for this subject. The following are additional comments about the cause of death and differential diagnosis of this subject. As previously described in the original review the differential diagnoses by the investigator included: convulsion, bronchospasm and respiratory failure, rule out pulmonary embolism. The treating physician in the patient's home town did not suspect drug overdose, poisoning (did not have any "signs or symptoms" of poisoning) and "his clinical diagnosis was: posticital stupor/postictal coma." The narrative also indicates that the treating physician gave a clinical diagnosis of "postictal stupor/postictal coma." "The investigator maintained that this event was probably related to study medication." While pulmonary embolism is a possible diagnosis it is not clear that this event actually occurred. Furthermore, other etiologies could have been due to an arrhythmia (e.g. secondary to QT prolongation), bronchospasm or other underlying events that could have been drug-related. An autopsy was not performed and other clinically relevant information (such as ECG results) was limited or could not be found in the narrative of this subject.

In conclusion no new clinical data (e.g. any diagnostic test results or autopsy results) on the above subject can be found that differs from clinical data that were previously described in the clinical review and clinical addendum review of NDA 21999 (other than the impression of the investigator on the cause of death). Consequently information on the above subject provided in the current submission does not change previous conclusions and recommendations conveyed by the undersigned reviewer in past clinical reviews of NDA 21999.

A Summary of Safety Results of Clinical Trials in the Previous 210-SUR Submission

The 210-SUR of NDA 21999 was not previously reviewed except for selected information that was summarized in previous clinical reviews of NDA 21999. [redacted]

Review Strategy of Updated Safety Information

For the purpose of the current review of this approvable response submission, only updated results of deaths, serious adverse events (SAEs) and adverse dropouts (ADOs) are reviewed and summarized (rather than providing more detailed safety results such as on clinical parameters). [redacted]

The clinical review of the original NDA 21999 (that include 120-Day SUR safety results) described the bulk of longterm safety data. This longterm data was primarily of the integrated OL extension trial safety dataset in which the sponsor had met ICH guidelines for exposure including 6 month and 12 month exposure (refer to results in the clinical review of the original NDA 21999 review). Only a few of the 6-12 month OL extension trials were ongoing since a review of the 120-Day SUR was completed and summarized in previous NDA 21999 reviews. Furthermore, limitations with OL data are inherent (as discussed in previous reviews).

In conclusion, for the purposes of the current review only updated information on deaths, SAEs and ADOs in ongoing trials (as summarized later) were reviewed and summarized below.

A more comprehensive review of other clinical safety results from selected safety datasets is currently being conducted [redacted]

Reviewer Conclusions on Results Described Below. *The safety results described below did not reveal any new, clinically remarkable findings that alter conclusions and recommendations that were previously conveyed in the original and addendum clinical reviews of NDA 21999.*

[redacted] Longterm Safety Results Relevant to the Current NDA 219999

As previously discussed the safety results on deaths, SAEs and ADOs below were also provided in the 210-Day SUR submitted under NDA 21999 [redacted]

The following summarizes the study design of open-label (OL) extension trials from which safety updated information was provided which includes ongoing trials and trials completed since the 120-Day SUR submission under NDA 21999. Other trials were previously completed in which deaths, SAEs and ADOs were previously provided and included in previous clinical reviews of NDA 21999.

OL Extension Trials: A brief summary of each OL Pal Extension trial is outlined below. All OL trails were conducted on patients with schizophrenia who previously participated in short-term efficacy Phase III trials. Each OL trial used a flexible dose design that generally allowed dose adjustments (generally in 3 mg intervals) to maximize efficacy while minimizing adverse events:

- Study -701 (non-elderly patients) used a 3-15 mg daily flexible-dose-level with a starting daily dose of 9 mg. This study is an OL extension trial that followed the maintenance treatment Phase III study -301. Study -301 was a pivotal maintenance trial [redacted] and was completed in time for inclusion of death, SAE and ADO information in the previously reviewed 120-Day SUR NDA 219999 submission.
- Elderly Study -702 used a 3-12 mg daily flexible-dose-level (3, 6, 9, or 12 mg/day) with a starting daily dose of 6 mg. This small 6-month OL extension trial followed the small, elderly, 6-week Phase III efficacy trial -302.
- Studies -703, -704 and -705 (almost all non-elderly patients). These studies used a 3-12 mg daily flexible-dose-level (3, 6, 9, or 12 mg/day), except for Study -305 which included a maximum daily dose level of 15 mg. The starting daily dose in these trials was 9 mg. In summary these trials included generally healthy adults, almost all non-elderly subjects with schizophrenia who had previously participated in a 6-week double-blind, placebo controlled, active (olanzapine) controlled, parallel group Phase III trial (Studies -302, -303, -304 and -305).

Pooled and Unpooled Safety Datasets that were Reviewed

The following summarizes the pooled and un-pooled safety datasets that are the focus of the safety review from which results described in sections below were obtained:

- Integrated OL Extension Trial Safety dataset (-702, -703, -704 and -705, combined).
- A Completed Extension OL Elderly Trial -702.
- A Completed Extension OL Study -701 that followed the maintenance treatment Study -301.

The Status of OL Extension Trials and Individual CSRs That Were Provided but Were Not Reviewed

- Status of OL trials as described in the submission are outlined below:
  - Study -705 is ongoing
  - Studies -702, -703 and -704 are now completed
- CSRs provided:
  - CSRs are provided for -701, -702 and -704 (since they were completed before the 2/1/06 cut-off date).
  - Study -703 was completed shortly after the cut-off date such that a CSR was not provided for this study. The CSR of Study -704 was provided but was not reviewed as described in the following.
- CSRs that were not reviewed:
  - The CSR of Study -701 was not reviewed. This study is the extension OL 12-month trial that followed Study -301. [redacted] included safety results from Study -701 that were selected for the purpose of this review and are summarized below. [redacted]
  - The CSR of Study -704 was not reviewed since the integrated OL trial safety database was reviewed and is considered to be more informative than a single OL trial that is a subset of the integrated safety dataset that the sponsor analyzed. Given the larger sample size and limitations inherent with data from OL trials, the integrated safety dataset is considered to be more likely to reveal a potential safety signal than a single trial from the integrated safety dataset.
  - Selected sections of the CSR of -702 were reviewed as described in sections below since this trial focused on a special population (elderly patients).

Updated Safety Information on Deaths, SAEs and ADOs
Excerpts on deaths, SAEs and ADOs described below are copied from Section 7 of the [redacted]

Deaths

Reviewer Comment. *To the knowledge of the undersigned reviewer and based on the information reviewed in the [redacted] submission, there are no newly reported deaths in clinical trials of Pal that were are not already described in the original and addendum clinical reviews of NDA 21999.*

Table 32: Deaths Through 1 February 2006
(Studies R076477-SCH-301, -701, -702, -703, -704, and -705)

Subject number (Study number)	Age (Years) Sex	Dictionary-derived Term Reported Term	Day of AE Onset[a]	Action Taken with Treatment	Relationship to Study Drug[b]
Double-Blind Study					
Treatment Group: ER OROS paliperidone (post run-in phase)					
100744 (R076477-SCH-301)	36 Male	Completed suicide death (suicide - strangulation by hanging)	72	None	Very likely
Treatment Group: Placebo					
100068 (R076477-SCH-301)	47 Male	Gun shot wound multiple gunshot wounds	174	None	Not related
100846 (R076477-SCH-301)	50 Male	Completed suicide suicide	152	None	Not related
Phase 3 Open-Label Extension Studies					
Treatment Group: Pla/Pali, ≤6 months					
200214 (R076477-SCH-702)	70 Male	Bronchopneumonia Bronchopneumonia	157[c]	None	Not related
Treatment Group: Pali/Pali, >6 months					
201516 (R076477-SCH-703)	42 Female	Completed suicide fall from 3rd floor	283	None	Not related
Treatment Group: Olan/Pali, >6 months					
200416 (R076477-SCH-703)	31 Female	Completed suicide suicide with medication[d]	238	None	Not related

[a] Study day is in reference to the start of double-blind medication, except for Subject 100744 (start of run-in phase).
[b] Relationship based on assessment of investigator.
[c] Subject was withdrawn from the study due to a serious adverse event (electrocardiogram QT corrected interval prolonged) and died of non-treatment-emergent bronchopneumonia 4 days after receiving the last dose of study medication.
[d] Subject ingested venlafaxine and lorazepam.

Between the cut-off dates of 2 February 2006 through 31 March 2006 an additional death was reported to occur in subject 100963 who was a 24 year old female with an unremarkable medical history who was only receiving trihexyphenidyl for extrapyramidal symptoms. The subject was lost to follow-up after receiving several months of 12 mg of paliperidone, daily during Study -701. She had experienced anxiety, dyspnea, vomiting followed by a seizure and ultimately cardiorespiratory arrest. A non-drug-related etiology could not be found in the narrative and an autopsy was not performed.

Reviewer Comment. *Subject 100963 was previously described in the original review of NDA 21999 and in an addendum review under NDA 21999 (subject [redacted] and 100963 are the same subject). In the absence of any clear etiology or risk factors (bronchospam or pulmonary embolism were considered in the differential diagnosis and the subject was a nonsmoker) or underlying conditions (no concomitant illnesses could be found in*

narrative descriptions), Pal treatment is highly suspected to be involved with events leading to death in this subject.

This subject had already received Pal treatment for months without prior related events (based on information found in the sponsor's response and in the safety alert report on this subject). Yet, adverse effects of pal including QT prolongation, cardiovascular effects, clinically remarkable changes in platelet count and hemoglobin, as examples among other observations are described in chronically treated subjects (refer to past clinical reviews of NDA 21999). However, limitations with the OL longterm safety data are inherent (refer to the original NDA 21999 review for details).

Other Serious Adverse Events

The following summary tables of the OL extension trials have updated information (as provided by the sponsor). Separate updated tables for each of the recently completed OL trials, studies -701 and -702 are also shown below (as provided by the sponsor).

Table 35: Serious Adverse Events Through 1 February 2006
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=11) N (%)	Pla/Pali >6 months (N=69) n (%)	Pali/Pali <=6 months (N=2) n (%)	Pali/Pali >6 months (N=70) n (%)	Pali(NO DB)/Pali <=6 months (N=22) n (%)	Pali(NO DB)/Pali >6 months (N=60) n (%)
Total no. subjects with serious adverse events	2 (18)	3 (4)	0	3 (4)	1 (4)	1 (2)
Psychiatric disorders	1 (9)	3 (4)	0	2 (3)	0	1 (2)
Schizophrenia	0	3 (4)	0	2 (3)	0	0
Delusion	0	0	0	0	0	1 (2)
Suicide attempt	1 (9)	0	0	0	0	0
Injury, poisoning and procedural complications	0	1 (1)	0	1 (1)	0	0
Alcohol poisoning	0	0	0	1 (1)	0	0
Tibia fracture	0	1 (1)	0	0	0	0
Nervous system disorders	1 (9)	0	0	0	0	0
Syncope	1 (9)	0	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	1 (4)	0
Varicocele	0	0	0	0	1 (4)	0

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 35: Serious Adverse Events Through 1 February 2006 (Continued)
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Total Pali <=6 months (N=36) n (%)	Total Pali >6 months (N=199) n (%)
Total no. subjects with serious adverse events	3 (8)	7 (4)
Psychiatric disorders	1 (3)	6 (3)
Schizophrenia	0	3 (2)
Delusion	0	1 (1)
Suicide attempt	1 (3)	0
Injury, poisoning and procedural complications	0	2 (1)
Alcohol poisoning	0	1 (1)
Tibia fracture	0	1 (1)
Nervous system disorders	1 (3)	0
Syncope	1 (3)	0
Reproductive system and breast disorders	1 (3)	0
Varicocele	1 (3)	0

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Table 21: Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term During the Open-Label Phase
(Study R076477-SCH-702: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali (N=30) n (%)	Pali/Pali (N=58) n (%)	Total (N=88) n (%)
Total no. of subjects with serious adverse event	2 (7)	3 (5)	5 (6)
Psychiatric disorders	1 (3)	2 (3)	3 (3)
Psychotic disorder	1 (3)	1 (2)	2 (2)
Schizophrenia	0	1 (2)	1 (1)
Blood and lymphatic system disorders	0	1 (2)	1 (1)
Anaemia	0	1 (2)	1 (1)
General disorders and administration site conditions	0	1 (2)	1 (1)
Pyrexia	0	1 (2)	1 (1)
Infections and infestations	0	1 (2)	1 (1)
Nasopharyngitis	0	1 (2)	1 (1)
Investigations	1 (3)	0	1 (1)
Electrocardiogram QTc interval prolonged	1 (3)	0	1 (1)

Table 36: Serious Adverse Events Through 3 February 2006
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Total no. subjects with serious adverse events	17 (17)	13 (9)	40 (19)	57 (12)	33 (31)	14 (10)	90 (22)	84 (11)
Psychiatric disorders	12 (12)	10 (7)	35 (17)	44 (9)	30 (28)	11 (8)	77 (19)	65 (9)
Psychotic disorder	7 (7)	2 (1)	14 (7)	20 (4)	12 (11)	5 (4)	33 (8)	27 (4)
Schizophrenia	2 (2)	3 (2)	15 (7)	15 (3)	13 (12)	3 (2)	30 (7)	21 (3)
Depression	0	2 (1)	1 (<1)	4 (1)	2 (2)	1 (1)	3 (1)	7 (1)
Suicidal ideation	2 (2)	1 (1)	3 (1)	4 (1)	0	0	5 (1)	5 (1)
Agitation	2 (2)	1 (1)	3 (1)	2 (<1)	5 (5)	1 (1)	10 (2)	4 (1)
Hallucination, auditory	0	0	0	4 (1)	0	0	0	4 (1)
Acute psychosis	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Anxiety	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Completed suicide	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Depressed mood	0	0	0	2 (<1)	0	0	0	2 (<1)
Suicide attempt	1 (1)	2 (1)	2 (1)	0	1 (1)	0	4 (1)	2 (<1)
Aggression	2 (2)	1 (1)	0	0	4 (4)	0	6 (1)	1 (<1)
Alcoholism	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Confusional state	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Delusion	0	0	2 (1)	1 (<1)	0	0	2 (<1)	1 (<1)
Insomnia	0	1 (1)	1 (<1)	0	2 (2)	0	3 (1)	1 (<1)
Paranoia	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Polydipsia psychogenic	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia, paranoid type	0	0	0	1 (<1)	0	0	0	1 (<1)
Self-injurious ideation	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
Infections and infestations	0	0	1 (<1)	8 (2)	1 (1)	1 (1)	2 (<1)	9 (1)
Nasopharyngitis	0	0	0	2 (<1)	0	0	0	2 (<1)
Bronchitis acute	0	0	0	1 (<1)	0	0	0	1 (<1)
Cellulitis	0	0	0	1 (<1)	0	0	0	1 (<1)

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 36: Serious Adverse Events Through 3 February 2006 (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Infections and infestations (continued)								
Measles	0	0	0	1 (<1)	0	0	0	1 (<1)
Perianal abscess	0	0	0	1 (<1)	0	0	0	1 (<1)
Pulmonary tuberculosis	0	0	0	0	0	1 (1)	0	1 (<1)
Sinusitis	0	0	0	1 (<1)	0	0	0	1 (<1)
Urinary tract infection	0	0	0	1 (<1)	0	0	0	1 (<1)
Hepatitis A	0	0	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	0	0	0	0	1 (1)	0	1 (<1)	0
Nervous system disorders	1 (1)	2 (1)	4 (2)	5 (1)	1 (1)	0	6 (1)	7 (1)
Akathisia	0	0	0	2 (<1)	1 (1)	0	1 (<1)	2 (<1)
Dizziness	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Dystonia	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Ischaemic stroke	0	1 (1)	0	0	0	0	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Transient ischaemic attack	1 (1)	0	0	0	0	0	1 (<1)	0
General disorders and administration site conditions	0	0	1 (<1)	4 (1)	1 (1)	0	2 (<1)	4 (1)
Pyrexia	0	0	0	2 (<1)	0	0	0	2 (<1)
Cyst	0	0	0	1 (<1)	0	0	0	1 (<1)
Irritability	0	0	0	1 (<1)	0	0	0	1 (<1)
Chills	0	0	1 (<1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0

See footnotes on the first page of the table.

Table 36: Serious Adverse Events Through 1 February 2006 (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Injury, poisoning and procedural complications	1 (1)	1 (1)	2 (1)	3 (1)	1 (1)	0	4 (1)	4 (1)
Alcohol poisoning	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Fall	0	0	0	1 (<1)	0	0	0	1 (<1)
Road traffic accident	0	1 (1)	0	0	0	0	0	1 (<1)
Traumatic haematoma	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Overdose	0	0	0	0	1 (1)	0	1 (<1)	0
Investigations	1 (1)	0	0	2 (<1)	0	0	1 (<1)	2 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Metabolism and nutrition disorders	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Diabetes mellitus	0	0	0	1 (<1)	0	0	0	1 (<1)
Hyponatraemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Hypokalaemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Benign neoplasm of skin	0	0	0	0	0	1 (1)	0	1 (<1)
Colon neoplasm	0	0	0	1 (<1)	0	0	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	0	0	1 (<1)	1 (<1)	0	1 (1)	1 (<1)	2 (<1)
Asthma	0	0	0	0	0	1 (1)	0	1 (<1)
Dyspnoea	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Pneumonia aspiration	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood and lymphatic system disorders	0	0	0	1 (<1)	0	0	0	1 (<1)
Anaemia	0	0	0	1 (<1)	0	0	0	1 (<1)

See footnotes on the first page of the table.

Table 36: Serious Adverse Events Through 1 February 2006 (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Gastrointestinal disorders	1 (1)	1 (1)	0	0	0	0	1 (<1)	1 (<1)
Crohn's disease	0	1 (1)	0	0	0	0	0	1 (<1)
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Hepatobiliary disorders	0	0	0	1 (<1)	0	0	0	1 (<1)
Cholelithiasis	0	0	0	1 (<1)	0	0	0	1 (<1)
Cardiac disorders	1 (1)	0	2 (1)	0	3 (2)	0	5 (1)	0
Bundle branch block	1 (1)	0	0	0	0	0	1 (<1)	0
Myocardial infarction	0	0	1 (<1)	0	0	0	1 (<1)	0
Sinus tachycardia	0	0	0	0	1 (1)	0	1 (<1)	0
Tachycardia	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Social circumstances	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Drug abuser	0	0	1 (<1)	0	2 (2)	0	3 (1)	0

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Additional SAEs Prior to the 4/1/06 Cut-off Date

The sponsor also specifies that 3 additional subjects had SAEs in the OL extension trials (of the combined OL extension trial dataset) since the cut-off date for the above summary table and prior to the 4/1/06 cut-off date. One of these subjects is subject 10096 who died (a 24 year old female with an unremarkable PMH who developed agitation, coma, convulsion and dyspnea and died during OL 12 mg daily Pal treatment). This subject was previously described under the section on deaths. The other 2 subjects had SAEs of

"exacerbation of schizophrenia" and "psychotic disorder and suicidal ideation," respectively.

Additional SAEs are described below.

Reviewer Comment.
No new clinically remarkable findings were revealed that change conclusions and recommendations that were previously described in the reviews of NDA 21999. The following are additional reviewer comments. .

OL Safety Dataset (Studies -701, through -705).
Results shown above are generally similar to results of the 120-Day SUR of NDA 21999 that were previously shown in the review of NDA 21999.

Newly reported SAEs (between November 1, 2005 in February 1, 2006), since the time of the four month safety update report were provided in the 210-Day safety update report of NDA 21999 (in the SCS section and line listing found in the appendix on page 1710 of this section) are identical to those provided in [redacted] the SCS of the current submission is identical to the SCS of the 210-Day SUR submission under NDA 21999, as specified on page 3 of the "Reviewer's Guide for [redacted] ; the line listing reviewed started on page 1710 of the 210-Day safety update report under NDA 21-999).

New SAEs reported before the most recent 4/1/06 cut-off date (3 subjects, as previously described) included 1 death that was also described in the review of NDA 21999. Information found on the other 2 subjects fail to shed any clinically new and remarkable findings that differ from those previously described in the review of NDA 21999.

Most SAEs in the line-listing (starting on page 1710 of the 210-Day SUR under NDA 21999) of newly reported SAEs were due to psychosis related SAEs and a few due to suicidal related SAEs. Few of these subjects had SAE and/or ADO Preferred or verbatim terms that included non-psychiatric related terms that might be considered unrelated to the psychiatric related event (e.g. none of these subjects had a cardiovascular related event reported as an ADO or SAE in addition to the psychiatric related SAE).

Psychiatric-related symptoms reported as SAE's and/or ADOs are expected for this patient population. However, it is theoretically possible to have exacerbation of symptoms secondary to underlying drug-related adverse effects (that could theoretically include non-psychiatric related adverse effects that may not be clearly expressed by an acutely psychotic or agitated patient). A description of such patients (i.e. patients of SAE's that could be reflecting a drug-related adverse effect) could not be found in in-text sections of the SCS section of this submission. The line listing that was found in the 210-Day safety update report under NDA 21999 (starting on page 1710) specified preferred

and verbatim terms for each ADO and SAE in a given subject. This line listing was reviewed. Subjects were found in this line listing that had a psychiatric-related SAE or ADO that had non-psychiatric-related verbatim terms reported either as an ADO or SAE term. The following subjects are noted:

- *Subject 100312 in Study -701 had SAE's of fracture of the left tibia (reported on Day 140 of the open-label extension phase, leading hospitalization) and "aggressive behavior" (reported during placebo double-blind treatment, with exacerbation of schizophrenia also reported SAE). "No information was available regarding the cause of the injury." However, given the events occurring during placebo treatment, it appears that this subject exhibits aggressive behaviors during an acute psychotic state which can increase the risk for injury. These events are not an uncommon event in this patient population. Exacerbation of schizophrenia was reported again as an SAE and was the event that led to an ADO in the subject.*
- *Subject 201432 had "exacerbation of schizophrenia" reported as an SAE who also had high fasting insulin levels, gastritis, candidiasis and high fasting c-peptide reported. These events were listed as SAEs in line listing but were indicated in a footnote as not being reported as serious but were instead "referenced to the clinical safety form." Several of these adverse events could be drug-related (e.g. diabetic mellitus-like adverse events are known to be associated with this drug-class) that may have contributed to worsening of schizophrenia.*
- *Subject 500772 with SAE's of akathisia, anxiety and irritability. Akathisia is known to occur with drugs in this drug-class and could lead to anxiety and irritability.*
- *Subject 501413 had confusion reported as an SAE (which could reflect a nonpsychiatric adverse effect). Agitation and acute psychotic episode were also reported as verbatim terms. Patients often appear to be confused while acutely psychotic and/or agitated. Information is limited in the narrative (e.g. does not mention results of a any possible neurological examination that might have been conducted while the patient was hospitalized, results of clinical parameters or diagnostic tests, and other relevant information such as orientation to person, time and place). These SAEs resolved as the patient continued OL treatment. However another psychotic episode was reported as an SAE (but confusion was not mentioned as an AE or SAE). This event lead to hospitalization which occurred over 200 days after the episode of confusion.*

The following non-psychiatric related SAEs are notable since a convincing or clear non-drug-related etiology could not be found and the events may reflect a new and remarkable drug-related effect on safety:

- *Subject 500501 had SAEs related to elevated LFTs (transaminases and GGT), as well as markedly elevated CPK (for unclear reasons). The subject was generally healthy (no non-drug-related etiology or risk factors were found in the narrative). These events were first noted on Day 160 of OL Pal (9 mg/day). LFTs remained elevated after 1 week of treatment cessation that may suggest a*

non-drug-related event, but levels were only provided for this one 1-week post treatment cessation time-point and LFT changes can sometimes lag behind changes in treatment. Elevations in LFT and CPK were previously described in this subject (refer to the original clinical review of NDA 21999 for details).

The following are additional comments regarding SAEs of Study -702 since this was the OL extension trial of elderly patients with schizophrenia (the study followed the elderly Phase III 6-week efficacy DB, placebo controlled trial, Study -302). Efficacy and safety results of Study -302 were previously described in the review of NDA 21999. However, Study -702 was ongoing at that time [redacted] provides the CSR for this OL elderly trial. A key difference on methodology of Study -702 (aside from the elderly age-group selected for the study) in contrast to the other OL extension trials (-703, -704, and -705) is that Study -702 involved 6 months of OL Pal treatment rather than a 12 month treatment phase.

Reviewer Comment and Results of a Completed Elderly OL Extension Trial
The previously shown table of SAEs for this elderly 6-month OL trial failed to show any remarkably new SAEs that were not previously observed or described in clinical reviews of NDA 21999 submission (and amendment submissions submitted prior to the PDUFA deadline for the first review cycle). A review of narratives also revealed that no new and clinically remarkable findings could be found that were not previously described in reviews of NDA 21999. The following are some additional comments on a few subjects.

The one subject 200326 who had multiple medical conditions and developed SAEs of anemia, pyrexia, nasopharyngitis leading to hospitalization had already completed the 6-week DB treatment phase and 20 days of OL Pal. This subject continued OL Pal during treatment of these SAEs. The SAEs resolved and completed OL Pal treatment in the study, such that a role of Pal is unlikely).

The subject that died 200214 was previously described under NDA 21999. This subject had a history of QT prolongation. The SAE and ADO of QTc prolongation was reported during OL treatment. The subject developed cough diagnosed as bronchopneumonia 2 days after the last dose and then died 4 days after the last dose. The "cause of death was reported as bronchopnuemia" and an autopsy was not performed. Other SAEs did not shed any new clinically remarkable findings that differ from those described in previous reviews of NDA 21999.

Dropouts and Other Significant Adverse Events

The following summary tables of OL trials provide updated information since the 120-Day SUR NDA 21999 submission since they include ongoing trials (tables were provided by the sponsor).

Table 39: Treatment-Emergent Adverse Events Leading to Study Discontinuation
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=11) n (%)	Pla/Pali >6 months (N=69) n (%)	Pali/Pali <=6 months (N=2) n (%)	Pali/Pali >6 months (N=70) n (%)	Pali(NO DB)/Pali <=6 months (N=23) n (%)	Pali(NO DB)/Pali >6 months (N=60) n (%)
Total no. subjects with adverse events	3 (27)	5 (7)	0	1 (1)	3 (13)	0
Psychiatric disorders	1 (9)	2 (3)	0	1 (1)	1 (4)	0
Anxiety	0	1 (1)	0	0	0	0
Depression	0	1 (1)	0	0	1 (4)	0
Schizophrenia	0	1 (1)	0	0	0	0
Suicidal ideation	0	0	0	1 (1)	0	0
Suicide attempt	1 (9)	0	0	0	0	0
Investigations	0	2 (3)	0	0	0	0
Electrocardiogram QT corrected interval prolonged	0	1 (1)	0	0	0	0
Electrocardiogram QT prolonged	0	1 (1)	0	0	0	0
Nervous system disorders	2 (18)	1 (1)	0	0	1 (4)	0
Dyskinesia	1 (9)	1 (1)	0	0	0	0
Dizziness	0	0	0	0	1 (4)	0
Syncope	1 (9)	0	0	0	0	0
Tremor	1 (9)	0	0	0	0	0
Gastrointestinal disorders	0	0	0	0	1 (4)	0
Vomiting	0	0	0	0	1 (4)	0
Reproductive system and breast disorders	0	0	0	0	1 (4)	0
Amenorrhoea	0	0	0	0	1 (4)	0

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 39: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Total Pali <=6 months (N=36) n (%)	Total Pali >6 months (N=199) n (%)
Total no. subjects with adverse events	6 (17)	6 (3)
Psychiatric disorders	2 (6)	3 (2)
Anxiety	0	1 (1)
Depression	1 (3)	1 (1)
Schizophrenia	0	1 (1)
Suicidal ideation	0	1 (1)
Suicide attempt	1 (3)	0
Investigations	0	2 (1)
Electrocardiogram QT corrected interval prolonged	0	1 (1)
Electrocardiogram QT prolonged	0	1 (1)
Nervous system disorders	3 (8)	1 (1)
Dyskinesia	1 (3)	1 (1)
Dizziness	1 (3)	0
Syncope	1 (3)	0
Tremor	1 (3)	0
Gastrointestinal disorders	1 (3)	0
Vomiting	1 (3)	0
Reproductive system and breast disorders	1 (3)	0
Amenorrhoea	1 (3)	0

See footnotes on the first page of the table.
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The following table is of the elderly OL extension trial (-702), as provided by the sponsor.

Table 22: Treatment-Emergent Adverse Events Leading to Study Discontinuation by MedDRA Preferred Term During the Open-Label Phase
(Study R076477-SCH-702: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali (N=30) n (%)	Pali/Pali (N=58) n (%)	Total (N=88) n (%)
Total no. of subjects who discontinued due to an adverse event	3 (10)	3 (5)	6 (7)
Investigations	1 (3)	1 (2)	2 (2)
Electrocardiogram QTc interval prolonged	1 (3)	0	1 (1)
Weight decreased	0	1 (2)	1 (1)
Psychiatric disorders	0	2 (3)	2 (2)
Confusional state	0	2 (3)	2 (2)
General disorders and administration site conditions	0	1 (2)	1 (1)
Fatigue	0	1 (2)	1 (1)
Infections and infestations	1 (3)	0	1 (1)
Pneumonia	1 (3)	0	1 (1)
Metabolism and nutrition disorders	0	1 (2)	1 (1)
Anorexia	0	1 (2)	1 (1)
Musculoskeletal and connective tissue disorders	1 (3)	0	1 (1)
Joint stiffness	1 (3)	0	1 (1)
Nervous system disorders	1 (3)	0	1 (1)
Tremor	1 (3)	0	1 (1)

Table 40: Treatment-Emergent Adverse Events Leading to Study Discontinuation
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=89) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Total no. subjects with adverse events	10 (10)	6 (4)	29 (14)	12 (3)	18 (17)	8 (6)	57 (14)	26 (3)
Psychiatric disorders	4 (4)	5 (4)	18 (9)	7 (1)	10 (9)	5 (4)	32 (8)	17 (2)
Depression	1 (1)	1 (1)	2 (1)	3 (1)	1 (1)	1 (1)	4 (1)	5 (1)
Psychotic disorder	2 (2)	0	2 (1)	1 (<1)	3 (3)	2 (1)	7 (2)	3 (<1)
Anxiety	0	1 (1)	0	0	1 (1)	1 (1)	1 (<1)	2 (<1)
Insomnia	0	0	3 (1)	1 (<1)	1 (1)	1 (1)	4 (1)	2 (<1)
Paranoia	0	2 (1)	1 (<1)	0	0	0	1 (<1)	2 (<1)
Acute psychosis	0	0	0	0	0	1 (1)	0	1 (<1)
Delusion	0	1 (1)	2 (1)	0	1 (1)	0	3 (1)	1 (<1)
Depressed mood	0	0	0	0	0	1 (1)	0	1 (<1)
Depressive symptom	0	1 (1)	0	0	0	0	0	1 (<1)
Polydipsia psychogenic	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia	0	0	2 (1)	1 (<1)	3 (3)	0	5 (1)	1 (<1)
Suicidal ideation	1 (1)	0	1 (<1)	1 (<1)	2 (2)	0	4 (1)	1 (<1)
Aggression	0	0	0	0	1 (1)	0	1 (<1)	0
Agitation	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Alcoholism	0	0	0	0	1 (1)	0	1 (<1)	0
Confusional state	0	0	3 (1)	0	0	0	3 (1)	0
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
Hallucination, auditory	0	0	1 (<1)	0	0	0	1 (<1)	0
Homicidal ideation	0	0	1 (<1)	0	0	0	1 (<1)	0
Hostility	0	0	1 (<1)	0	0	0	1 (<1)	0
Suicide attempt	0	0	1 (<1)	0	0	0	1 (<1)	0
Nervous system disorders	1 (1)	1 (1)	6 (3)	1 (<1)	2 (2)	3 (2)	9 (2)	5 (1)
Akathisia	0	0	2 (1)	0	0	2 (1)	2 (<1)	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Dyskinesia	0	1 (1)	0	0	0	0	0	1 (<1)
Extrapyramidal disorder	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 40: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Nervous system disorders (continued)								
Hypertonia	0	0	0	0	0	1 (1)	0	1 (<1)
Mental impairment	0	0	0	0	0	1 (1)	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dizziness	0	0	0	0	2 (2)	0	2 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Dystonia	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Tremor	1 (1)	0	0	0	0	0	1 (<1)	0
Investigations	1 (1)	1 (1)	1 (<1)	3 (1)	2 (2)	0	4 (1)	4 (1)
Weight increased	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Alanine aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Aspartate aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood prolactin increased	0	1 (1)	0	0	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Gamma-glutamyltransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram T wave abnormal	0	0	0	0	1 (1)	0	1 (<1)	0
Hepatic enzyme increased	0	0	0	0	1 (1)	0	1 (<1)	0
Weight decreased	0	0	1 (<1)	0	0	0	1 (<1)	0
Reproductive system and breast disorders	0	0	2 (1)	1 (<1)	0	1 (1)	2 (<1)	2 (<1)
Erectile dysfunction	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Galactorrhoea	0	0	0	0	0	1 (1)	0	1 (<1)
Retrograde ejaculation	0	0	1 (<1)	0	0	0	1 (<1)	0

See footnotes on the first page of the table.

Table 40: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Injury, poisoning and procedural complications	1 (1)	0	2 (1)	1 (<1)	0	0	3 (1)	1 (<1)
Traumatic haematoma	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Self mutilation	1 (1)	0	0	0	0	0	1 (<1)	0
Metabolism and nutrition disorders	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Hyponatraemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Anorexia	0	0	1 (<1)	0	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Pneumonia aspiration	0	0	0	1 (<1)	0	0	0	1 (<1)
Dyspnoea	0	0	1 (<1)	0	0	0	1 (<1)	0
Cardiac disorders	1 (1)	0	3 (1)	0	2 (2)	0	6 (1)	0
Myocardial infarction	0	0	1 (<1)	0	0	0	1 (<1)	0
Myocardial ischaemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Palpitations	0	0	0	0	1 (1)	0	1 (<1)	0
Sinus tachycardia	1 (1)	0	0	0	1 (1)	0	2 (<1)	0
Tachycardia	0	0	1 (<1)	0	0	0	1 (<1)	0
Eye disorders	0	0	0	0	1 (1)	0	1 (<1)	0
Vision blurred	0	0	0	0	1 (1)	0	1 (<1)	0
Gastrointestinal disorders	1 (1)	0	1 (<1)	0	3 (3)	0	5 (1)	0
Constipation	0	0	0	0	1 (1)	0	1 (<1)	0
Dysphagia	0	0	1 (<1)	0	0	0	1 (<1)	0
Nausea	0	0	0	0	1 (1)	0	1 (<1)	0
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Vomiting	0	0	0	0	2 (2)	0	2 (<1)	0

See footnotes on the first page of the table.

Table 40: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
General disorders and administration site conditions	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Fatigue	0	0	1 (<1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0
Infections and infestations	1 (1)	0	1 (<1)	0	0	0	2 (<1)	0
Hepatitis A	0	0	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	1 (1)	0	0	0	0	0	1 (<1)	0
Musculoskeletal and connective tissue disorders	1 (1)	0	1 (<1)	0	2 (2)	0	4 (1)	0
Arthralgia	0	0	0	0	1 (1)	0	1 (<1)	0
Joint stiffness	1 (1)	0	0	0	0	0	1 (<1)	0
Muscle rigidity	0	0	1 (<1)	0	0	0	1 (<1)	0
Muscle twitching	0	0	0	0	1 (1)	0	1 (<1)	0
Skin and subcutaneous tissue disorders	0	0	1 (<1)	0	0	0	1 (<1)	0
Acne	0	0	1 (<1)	0	0	0	1 (<1)	0
Social circumstances	0	0	2 (1)	0	2 (2)	0	4 (1)	0
Alcohol use	0	0	1 (<1)	0	0	0	1 (<1)	0
Drug abuser	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Vascular disorders	0	0	0	0	1 (1)	0	1 (<1)	0
Hypertension	0	0	0	0	1 (1)	0	1 (<1)	0

See footnotes on the first page of the table.
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126

Reviewer Comments.

Study -701

Updated results fail reveal any new clinically remarkable findings that differ from results described in reviews of NDA 21999 (the review of the original NDA submission and the addendum review).

The following subjects are noted and were not previously noted in the review of the original NDA 21999 submission:

- *Subject 100756: this 44-year-old female was an ADO due to QTc prolongation (severe) of up to 462 and 460 milliseconds for QTc F and QTc LD, respectively. QTc prolongation for QTc F was first noted during the run-in phase, apparently on Day 57 while receiving 15 mg of paliperidone (QTc B was noted sooner during Pal treatment, but is not considered an accurate calculation method for QT since a heart rate was not described as being abnormally low). Pal treatment was terminated due to QT prolongation. QTcLD normalized while QTcF decreased to 451 milliseconds on Day 7 after cessation of Pal.*

  QT prolongation this subject is likely to be drug-related due to the following reasons. A non-drug-related etiology was not identified. Also the timing of this event that resolved after treatment cessation, as well as QT prolongation effects observed with Pal (as revealed in Phase three trials and in an EKG study which is described in the review of the original NDA 21999),

Pooled OL Trials (-702,-703,-704,-705)

No new clinically remarkable findings were revealed that differ from results previously described in the review and addendum review of NDA 21999.

Newly reported ADOs since the time of the four month safety update report were provided in the 210-Day safety update report of NDA 21999 (in the SCS section and line listing found in the appendix of this section, starting on page 1710). [redacted]

See previous comments on psychiatric related SAEs that also apply to psychiatric related AEs leading to ADOs.

The following non-psychiatric related ADOs are described, since a clear non-drug-related etiology could not be found and the event(s) may reflect a new, potentially remarkable drug-related effect on safety:

- *Subject 501535 had increased hepatic enzymes reported as an AE leading to an ADO who had abnormal values at baseline. However, the subject showed more marked elevations in GGT during DB olanzapine and OL pal treatment and had treatment discontinued on Day 5 of OL Pal (9 mg/day). Levels remained elevated on Day 6. No other information could be found in the narrative regarding any subsequent levels, non-drug-related etiologies or risk factors. Additional cases of subjects with elevated LFTs and ADOs due to elevated LFTs were previously described in the previous clinical reviews of NDA 21999.*
- *Subject 100921(previously received placebo in the lead-in study) had QTc prolongation leading to an ADO, that did not appear to be drug-related since similar QTc values were observed during placebo treatment in the lead-in study.*
- *Subject 100943 had junction nodal rhythm that lead to an ADO that was first noted on Day 42 of 9 mg Pal daily (during the run-in phase) that was not reported at baseline or upon treatment cessation ("resolved" post-treatment-cessation). A cardiologist in the central laboratory read the same ECG and reported it as normal. Paliperidone treatment was discontinued after two days of 12 mg of daily paliperidone during the open-label these study-701 due to "nodal rhythm" that was reported "as persisting." Incomplete right bundle branch block was reported at baseline and at post treatment cessation. Ranitidine was given on Day 42 for dyspepsia. This subject was a 30 year old healthy female with a past medical history of anemia and respiratory infection.*

The role of Pal is considered probable in the absence of more information. Despite a normal reading by the cardiologist on Day 42, the event was considered persisting several days later, in which EKG results that lead to this conclusion could not be found in the narrative description. The description of a cardiology work-up of the patient during or following the study or any mention of holter monitoring (which would have been helpful at least following treatment cessation) could not be found in the narrative description of this subject.

A higher incidence of first degree AV block compared to placebo was previous observed in the 15 mg Pal treated subjects in the integrated 6-week Phase III trial safety dataset and in elderly Pal treated subjects in the 6-week Phase III Study -302.

- *Subject 500501 had SAE's involving elevated liver function tests and elevated CPK that lead to an ADO of this subject. This subject was previously described under the above section on SAE's and was also previously described in past clinical reviews of NDA 21999.*
- *Subject 500507 had elevations in liver function tests, but these elevations are also observed at baseline with no further increase observed during olanzapine and paliperidone treatment (this subject received double-blind olanzapine during Study-305 followed by open label paliperidone during Study-705). Since the LFT elevations persisted, the subject was withdrawn prematurely due to AEs of elevated LFTs (an ADO). His LFTs declined upon dechallenge. This subject was not previously described in the original clinical review of NDA 21999. However, similar cases were previously described.*
- *Subject 501535 had hepatic enzymes increased (ALT, AST, and GGT) reported as an ADO who had abnormal levels at baseline but had markedly greater elevations in gamma-glutamyltransferase levels during double-blind olanzapine treatment (on Day 21 of the double-blind lead-in Study-305). The subject continued to show elevations after five days of open label treatment with 9 mg, daily of paliperidone in Study-705 and was therefore discontinued from the study on Day 6.*

  This subject had an unremarkable past medical history, did not receive concomitant medications and an etiology for these events, or a potential etiology and other relevant information (e.g. mention or results of a diagnostic work-up) could not be found in the narrative description. This subject was not previously described in the original clinical review of NDA 21999. However, other subjects with elevated LFTs and ADOs due to hepatic-related AEs were previously described in past clinical reviews of NDA21999.

Psychiatric-related ADOs that were also associated with non-psychiatric related SAE's or ADOs are previously discussed in the section on SAEs above.

Results and Reviewer Comments of Elderly OL Trial -702

The summary table of ADOs, as previously shown, includes isolated ADOs of anorexia and joint stiffness but these isolated cases do not change overall conclusions on safety or on the overall safety profile of Paliperidone in this population, as previously discussed in the review of NDA 21999. Additional ADOs are described below, that do not change the overall safety profile as previously described in clinical reviews of NDA 21999.

Due to the unexpected ADOs of confusion in 2 subjects (200321 and 200719), a review of the narratives of these subjects was conducted. It appears these subjects had a pre-existing condition that was likely to at least play a role in the development of confusion.

However, a clear diagnosis of dementia (e.g. with supporting diagnostic testing) could not be found in the narratives. These subjects are described in more detail later. One consideration is a possible role of Pal exacerbating underlying dementia-like conditions in these elderly subjects. Pal is not indicated for dementia and the sponsor is only seeking a schizophrenia indication. Furthermore, proposed labeling includes a drug class section on risk of mortality with patients with dementia.

A review of the narrative of an atypical ADO of joint stiffness (subject 200412) was also conducted. This event occurred in a women receiving thyroid replacement hormone for hypothyroidism. She developed tremor in the same arm where she developed stiffness (in the elbow). Consequently a role of Pal is likely since tremor is an expected extrapyramidal side effect that in turn was likely to contribute to the joint stiffness. A role of the patient's age, along with thyroid disease may also have contributed to this AE.

The sponsor's in-text description of the ADO due to anorexia (subject 200309 as found in the CSR) did not describe any other abnormalities in this subject other than anorexia and weight loss. This subject was not reported to have any pre-existing condition. Although acute psychosis, as well as the patient's age could be factors involved with this AE, a role of Pal is suggested since a non-drug-related etiology cannot be clearly identified.

The sponsor provided in-text descriptions of selected subjects in the CSR of -702. These descriptions are summarized below. Some of these subjects were previously noted above.

DB-Placebo/OL-Pal Treated Subjects with ADOs in Study -702.
These subjects previously received DB Placebo in the 6-week Phase III lead-in study to the OL Pal Extension Study -702:

- **Subject 200214:** with the SAE of QTc prolongation. This subject was previously described in this review as a subject who died with cause of death, reported as bronchopneumonia.
- **Subject 200412:** a 71-year old female who had a medical history of hypothyroidism being treated with levothyroxine sodium and had joint stiffness and tremor on OL Pal treatment Day 15 leading to an ADO on Day 21. Comments on this subject were previously provided.
- **Subject 200713:** a 66-year old male with pneumonia leading to an ADO on Day 31 of OL al had a history of pulmonary tuberculosis, pneumonia (twice) and chronic bronchitis.

DB-Pal/OL-Pal Treated Subjects with ADOs in Study -702
These subjects previously received DB Pal in the 6-week Phase III lead-in study to the OL Pal Extension Study -702:

- **Subject 200309**, had ADOs of anorexia and decreased weight (from 41 kg prior to treatment to 41 kg on Day 73 of OL treatment when Pal was stopped). This subject was previously noted.
- **Subject 200321:** a 74-year old female with a history "noted dementia-like symptoms, but no formal diagnosis" and was receiving 4 mg BID of galantamine for "dementia-like symptoms," and dihydroergotamine (2 mg/day) for mild hypotension. The dose of during the OL phase due to "moderate hypotension." During OL treatment events of confusion, fatigue, insomnia and hypotension (this resolved with an increase in dihydroergotamine to 2.5 mg bid). Confusion and fatigue worsened and the confusion lead to the ADO. This subject was previously noted.
- **Subject 200719** a 65-year old female who had a history of "cerebrosclerosis." She had an AE of insomnia that persisted and later developed confusion which worsened such that Pal treatment was stopped. The subject was previously noted.

E. Post Approval (Postmarketing) Clinical Commitments
We note that in the one study that included a 3 mg dose of paliperidone ER, that dose was shown to be effective. Thus, you have not fully evaluated the lower end of the dose response curve. Therefore, you should conduct a study to better explore for a minimal effective dose in phase IV.

The sponsor agrees to this commitment as follows (as copied from their response submission):

J&JPRD agrees to perform a study to better assess the lower end of the dose response curve and can perform an efficacy study of 1.5 mg paliperidone ER tablets in subjects with schizophrenia as a Phase 4 commitment. The Sponsor proposes to submit a protocol for such a study to the Agency for review within 3 months after approval. We estimate a study report could be submitted by December 2010.

Reviewer Comments. *The sponsor has adequately responded to this item in the Approvable letter on Phase IV commitment. Once the sponsor submits a protocol the Division can provide feedback on the study design, as deemed appropriate.*

F. Labeling
Please submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Sponsor's Response and Reviewer Comments
The purpose of this labeling review is to address the sponsor's proposed changes in clinical sections of labeling that differ from labeling provided in the Approvable Action Letter. Therefore this review does not repeat past issues and recommendations that were previously raised in past clinical reviews under NDA 21999 (the original and addendum reviews). The draft-annot-labeling-text.pdf file in the current submission was used to review clinical sections of labeling changes proposed by the sponsor as specified in this pdf file (the sponsor used track changes to denote changes made from the version provided in the Approvable letter).

Proposed modifications of clinical labeling sections are generally presented in this review in the order in which they appear in the sponsor's proposed labeling, unless there are related sections that appear elsewhere in labeling on a given topic or issue being discussed in this review.

Other labeling changes that are proposed by the sponsor are under review by other disciplines (these reviews are pending at the time of this writing).

31 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

G. Conclusions and Additional Recommendations

Safety results described in this review failed to reveal any safety-related observations that would change conclusions and recommendations in the original review of NDA 21999.

The sponsor has also adequately responded to the Clinical items in the Approvable Action letter but has made revisions in labeling that differ from labeling in the Approvable Letter. See specific labeling recommendations in the Labeling section of this review.

In addition to labeling recommendations, the following are additional recommendations.

Word-for-Word Comparisons between Labeling Versions are Recommended

In addition to labeling issues raised in this review, it is also recommended that word-for-word comparisons be conducted between the sponsor's proposed labeling and the Approvable Action letter version of labeling. The "draft-annot-labeling-text.pdf" file was used for purposes of this review. If differences are found in any of the above word-to-word comparisons then it is recommended that the sponsor be notified of these differences and inquired about them. In the opinion of the undersigned reviewer, a convincing rationale would need to be provided for any differences that are found unless they are minor editorial differences that do not impact on the content of the information and would not be expected to alter the interpretation of the information being conveyed from a clinical perspective.

It is also recommended that word-to-word comparisons of drug class labeling sections under Warnings and Precautions of the sponsor's proposed labeling be made with corresponding sections of approved drugs (e.g. Risperdol®). If differences are found then it is recommended that labeling be revised to match standard language for the drug class, unless the sponsor provides a convincing rationale for changing drug class labeling language.

Karen Brugge, M.D.
Medical Reviewer,
FDA CDER ODE1 DPP HFD 130

cc: IND; HFD 130/N Khin/K Brugge/K Kiedrow/T Laughren/M Mathis/F Fanhui/P Yang/B Rosloff/R Baweja/R Kavanagh/T Oliver/C Tele/E Chalecka-Franaszek

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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2

Table 8: Treatment-Emergent Adverse Events With at Least 2% Incidence in Any Paliperidone Treatment Group (3 or 6 or 9 or 12 or 15) and Where the Incidence > Placebo by MedDRA Preferred Term - Double-Blind Phase
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Placebo (N=533) n (%)	ER ORDS Paliperidone 3 mg (N=157) n (%)	6 mg (N=251) n (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)	15 mg (N=115) n (%)	Olanzapine 10 mg (N=364) n (%)
Nervous system disorders	96 (27.0)	34 (26.8)	68 (28.9)	99 (40.2)	110 (45.5)	47 (41.6)	123 (33.8)
Akathisia	14 (3.9)	5 (3.9)	7 (3.0)	20 (8.1)	23 (9.5)	11 (9.7)	7 (1.9)
Dizziness	14 (3.9)	7 (5.5)	11 (4.7)	11 (4.5)	12 (5.0)	7 (6.2)	19 (5.2)
Dystonia	2 (0.6)	1 (0.8)	3 (1.3)	9 (3.7)	9 (3.7)	1 (0.9)	1 (0.3)
Extrapyramidal disorder	8 (2.3)	6 (4.7)	5 (2.1)	17 (6.9)	18 (7.4)	9 (8.0)	6 (1.6)
Headache	42 (11.8)	14 (11.0)	29 (12.3)	34 (13.8)	36 (14.9)	20 (17.7)	35 (9.6)
Hypertonia	4 (1.1)	3 (2.4)	3 (1.3)	10 (4.1)	8 (3.3)	4 (3.5)	5 (1.4)
Parkinsonism	0	0	1 (0.4)	5 (2.0)	3 (1.2)	2 (1.8)	2 (0.5)
Sedation	13 (3.7)	1 (0.8)	12 (5.1)	8 (3.3)	15 (6.2)	2 (1.8)	24 (6.6)
Somnolence	13 (3.4)	6 (4.7)	8 (3.4)	17 (6.9)	11 (4.5)	7 (6.2)	47 (12.9)
Tremor	12 (3.4)	4 (3.1)	6 (2.6)	11 (4.5)	8 (3.3)	3 (2.7)	8 (2.2)
Psychiatric disorders	111 (31.3)	33 (26.0)	59 (25.1)	61 (24.8)	57 (23.6)	33 (29.2)	96 (26.4)
Anxiety	29 (8.2)	12 (9.4)	16 (6.8)	14 (5.7)	11 (4.5)	9 (8.0)	21 (5.8)
Sleep disorder	2 (0.6)	1 (0.8)	1 (0.4)	3 (1.2)	1 (0.4)	4 (3.5)	4 (1.1)
Suicidal ideation	4 (1.1)	2 (1.6)	2 (0.9)	1 (0.4)	1 (0.4)	3 (2.7)	3 (0.8)
Respiratory, thoracic and mediastinal disorders	14 (3.9)	8 (6.3)	11 (4.7)	13 (5.3)	10 (4.1)	11 (9.7)	21 (5.8)
Cough	4 (1.1)	4 (3.1)	4 (1.7)	7 (2.8)	4 (1.7)	3 (2.7)	6 (1.6)
Nasal congestion	3 (0.8)	1 (0.8)	3 (1.3)	2 (0.8)	2 (0.8)	3 (2.7)	3 (0.8)
Vascular disorders	10 (2.8)	5 (3.9)	9 (3.8)	9 (3.7)	15 (6.2)	6 (5.3)	14 (3.8)
Orthostatic hypotension	3 (0.8)	3 (2.4)	3 (1.3)	5 (2.4)	9 (3.7)	3 (2.7)	6 (1.6)

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/s/

Karen Brugge
11/20/2006 11:20:25 AM
MEDICAL OFFICER

Mitchell Mathis
11/21/2006 06:26:57 PM
MEDICAL OFFICER

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 22, 2006

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable action for paliperidone ER tablets for schizophrenia (short-term efficacy only)

TO: File NDA 21-999
[Note: This overview should be filed with the 11-30-05 original submission of this NDA.]

1.0 BACKGROUND

Paliperidone ER is an extended release formulation of paliperidone, an atypical antipsychotic (5HT2 and D2 receptor antagonist). It is the major active metabolite of risperidone and has essentially the same pharmacological profile as risperidone which is approved for the treatment of schizophrenia and bipolar mania. This NDA seeks a claim for the short-term treatment of schizophrenia, in a dose range of 3 to 12 mg/day.

Paliperidone ER was developed under IND 65,850. We held a number of meetings with the sponsor of this IND during the development of paliperidone ER, and had planned on taking it to the PDAC. However, as we neared the end of the review cycle, we decided that there were no critical review issues that needed input from the PDAC.

2.0 CHEMISTRY

I am not aware of any CMC issues at this point that would preclude an approvable action for this NDA.

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology issues at this point that would preclude an approvable action for this NDA. We are relying on the carcinogenicity data for the parent drug,

risperidone, because of adequate exposure to paliperidone and its metabolites in those studies. There was a question about possibly different human metabolites seen with paliperidone administration compared to what is seen with risperidone administration, however, to my knowledge, this concern has been addressed and we do not believe there are any new metabolites with paliperidone administration.

4.0 BIOPHARMACEUTICS

Paliperidone ER is an OROS formulation of paliperidone that reaches Cmax in about 24 hours and has an average elimination half-life of approximately 23 hours. Thus, steady state is reached in about 4-5 days. There is a substantial food effect, with Cmax and AUC values increased by roughly 50% in the fed state. However, the clinical trials with paliperidone ER were carried out without regard to food intake. Paliperidone ER has minimal peak-trough fluctuations compared to immediate release risperidone. Although both 2D6 and 3A4 appear to have some role in metabolizing paliperidone ER, it is not extenisively metabolized in the liver. Rather, it is substantially cleared unchanged in the urine.

I am not aware of any biopharmaceutics issues at this point that would preclude an approvable action for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of this application focused on 4 short-term (6-week), double-blind, randomized, parallel group, placebo-controlled trials in patients with acutely exacerbated schizophrenia. The primary endpoint was change from baseline on the PANSS total score. Treatment group sizes in the adult studies ranged from 105 to 128 patients per group. Three studies were fixed-dose, active controlled (olanzapine 10 mg) studies in adults (303, 304, and 305) and the fourth was a flexible-dose study (3-12 mg/day) in elderly schizophrenic patients (302). Study 304 was conducted entirely in the US. Dosing was always AM, without regard to meals.

The fixed paliperidone ER doses in the adult studies were as follows:

Study #	Dose Groups			
303	6 mg	9 mg	12 mg	
304	6 mg		12 mg	
305	3 mg	9 mg		15 mg

In summary, for the adult studies, all doses studied were statistically significantly superior to placebo, and the effect sizes were typical of those seen with effective antipsychotic drugs. There was a slight numerical advantage to the higher doses compared to the lower doses, and in some but not all comparisons, these differences were statistically significant. Thus, unlike the data for risperidone, there may be some advantage to higher doses compared to lower doses. As can be seen, there are data from only 1 trial supporting the 3 mg/day dose.

The elderly flexible-dose study showed a trend for drug superiority, but was likely underpowered.

5.1.3 Comment on Other Important Clinical Issues Regarding the Paliperidone ER Efficacy Data

Evidence Bearing on the Question of Dose/Response for Efficacy

As noted, there was a numerical trend for dose response, and some statistical evidence to support dose response as well. The sponsor has proposed 6 mg/day as the target dose, with the possibility of titration within a range of 3-12 mg/day, at the judgment of the clinician. Dr. Brugge has agreed with this proposal, while Dr. Khin has suggested targeting 3 mg/day. Given the fact that there is some support for dose response, and more data for doses in the 6-12 mg/day range than the 3 mg/day dose, I am inclined to accept 6 mg/day as the target dose for now. However, I agree with Dr. Khin that the sponsor should be asked to commit to a fixed dose study at the lower end of the dose response curve to better establish efficacy at the lower end.

Secondary Efficacy Variables

In their proposed labeling, the sponsor has added results from the PANSS factors as well as from the PSP (Personal and Social Performance) scale. Even if declared in the protocol as key secondaries, we would not have accepted the PANSS factors because they are redundant with the total score. However, we did in fact communicate to the sponsor in an earlier meeting that the PSP would be acceptable as a key secondary, since we consider it a reasonable measure of functional improvement. Oddly, however, the sponsor did not clearly specify the PSP as a key secondary, nor provide a clearly defined analysis plan for addressing the PSP and multiple doses. Thus, they will not be permitted to include the results from either secondary outcome in their labeling.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis primarily of gender, because there were not sufficient data to explore differences based on age or race. There was no indication of any difference in effectiveness based on gender.

Size of Treatment Effect

The effect sizes observed in these trials were similar to those seen in other positive schizophrenia trials.

Duration of Treatment

The sponsor presented no data pertinent to longer-term efficacy in this NDA, [redacted]

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy of paliperidone ER in the treatment of schizophrenia.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for this NDA were derived from a total of n=2115 subjects/patients exposed to paliperidone ER across 37 clinical trials comprising the total paliperidone ER program. The patient breakdown included n=592 paliperidone ER-exposed subjects/patients in 27 phase 1/2 trials, and n=1523 paliperidone ER-exposed patients in 10 phase 3 trials. This represents about 508 patient-years of exposure. They easily satisfied ICH criteria for long-term exposure.

5.2.2 Common Adverse Event Profile for Paliperidone ER in Schizophrenia

The profile of common and drug-related adverse events included: tachycardia; akathisia; EPS; dystonia; hypertonia; orthostatic hypotension; and hypersalivation. Thus, paliperidone ER has an adverse event profile quite similar to that seen for risperidone, as would be expected.

5.2.3 Adverse Events of Particular Interest

5.2.3.1 Orthostatic Hypotension and Syncope

Paliperidone ER has alpha-adrenergic blocking activity, thus, it is no surprise that there is drug-related and dose-related orthostatic hypotension seen with this drug, as is the case with risperidone. However, the effect is modest. As an adverse event, orthostatic hypotension was seen in 2% of drug-treated patients in the pool of adult phase 3 trials compared to 1% of placebo (higher at the higher doses, e.g., 4% at 12 mg). As a measured orthostatic change, it was observed in 7% of drug-treated vs 4% of placebo-treated patients. Syncope was also a drug-related event (0.8% in drug vs 0.3% in placebo). The sponsor has proposed a Precautions

statement similar to the statement in risperidone labeling to address this concern, and I think this is adequate.

5.2.3.2 Tachycardia

It is also no surprise that there is drug-related and dose-related tachycardia seen with this drug, as is the case with risperidone. As an adverse event, tachycardia was dose-related, with rates of about 7% at the higher doses in the pool of adult phase 3 trials compared to 3% of placebo patients. There was also a dose-related mean increase in heart rate, i.e., about 7 bpm at the higher doses vs about 2 bpm in placebo-treated patients. Tachycardia is clearly noted in labeling as a drug-related effect.

5.2.3.3 QTc Increases

Although there is not a QTc signal emerging from the phase 3 trials with paliperidone ER, which included extensive ECG monitoring, there is a modest signal emerging from the sponsor's thorough QT study (SCH-1009) involving an immediate release formulation of paliperidone (on the order of a 10 msec increase from baseline at exposures that are likely to be seen at the higher recommended doses of paliperidone ER). Given the roughly 50% increase in paliperidone exposures when the ER formulation is given with a high fat meal, the Division of Cardiorenal Products (DCRP) has recommended that paliperidone ER not be given with food. However, the data from study SCH-1009 seem to suggest a plateau of the exposure response curve for QTc effect:

Paliperidone IR Dose	Exposure	QTc Increase from Baseline
4 mg	35 ng/ml	9.3 msec
8 mg	113 ng/ml	10.9 msec

Given that the expected Cmax ss for the 12 mg paliperidone ER dose (the maximum recommended dose) is only 45 ng/ml, a 50% increase with a high fat meal would yield an exposure well below the exposure seen with 8 mg IR. Thus, I am not inclined to recommend dosing only in the fasted state. Furthermore, this advice would be virtually impossible to implement with this population. The currently proposed Dosage and Administration section alerts prescribers to the increased exposure occurring with a high fat meal, and I think this is sufficient.

I do agree with DCRP's recommendation that the language in labeling regarding QTc prolongation be revised and relocated to Warnings. The sponsor relied on a day-averaged value for QTc increase, which underestimates the effect at peak concentration, a more appropriate measure. Our proposed language for this statement will alert prescriber's to a possible risk of torsade de pointes and/or sudden death with this drug, and will warn against certain situations that may increase this risk.

One puzzling fact is that we have not seen a signal for a similar degree of QTc prolongation with the parent drug, risperidone, even in a similarly thorough QT study (study 54 conducted by Pfizer), even though the expected levels of paliperidone would be similar to those observed in study SCH-1009.

5.2.3.4 Hyperprolactinemia

As expected, paliperidone ER elevates prolactin, and in fact, the extent of elevation seen with this drug is very similar to that seen with risperidone. Given that risperidone is an outlier among atypical antipsychotics in terms of its potential for elevating prolactin, and we have recently asked the sponsor to strengthen the labeling for risperidone regarding this effect. I agree with Dr. Khin that we need to ask the sponsor to adopt similar language for paliperidone ER.

5.2.4 Other Concerns of Dr. Brugge

5.2.4.1 CPK Elevations

Dr. Brugge seems concerned about some paliperidone-treated patients with CPK increases. However, the placebo-controlled trial data reveal no signal for drug-related CPK increases, and I do not agree that the sponsor needs to do more to evaluate this concern.

5.2.4.2 Suicidality

Dr. Brugge argues that more should be done to evaluate suicidality with paliperidone ER, however, her concern is not supported by the available data. In the pool of placebo-controlled phase 3 trials, the risk of suicidality using an approach that seems quite reasonable to me is about 1% for both drug and placebo. Thus, I agree with Dr. Khin that the sponsor's proposal to include the standard suicidality language for antipsychotic drugs is reasonable.

5.2.4.3 Food Effect

Dr. Brugge also argues that more needs to be done to evaluate the impact of a food effect, however, I don't agree. I think the food effect (approximately 50% increase in Cmax and AUC in the fed state) has been well-characterized and also adequately studied, in the sense that drug was given without regard to food intake in the clinical program. Thus, the adverse event profile observed reflects the conditions of use, and that profile has been well-characterized in labeling, in my view.

5.2.4.4 "Hemodynamic Effects"

Dr. Brugge repeatedly raises concerns about "hemodynamic" effects of paliperidone, however, it isn't clear what she means by this, beyond the quite predictable hypotensive effects, the tachycardia, and the demonstrated modest QTc effect. She recommends a number of phase 4 commitments to address these concerns, including drug interaction studies with other drugs that

prolong the QTc, tread mill tests, tilt table tests, chronic open label challenge studies with higher than recommended doses of paliperidone, among others. I don't see any merit in any of these studies, and I will not be making such recommendations. I feel that the observed effects of paliperidone on blood pressure, heart rate, and the QTc can be adequately characterized in labeling.

5.2.3.5 Gastrointestinal Problems Related to OROS Capsule

Dr. Brugge has noted a very small but clinically meaningless reduction in hemoglobin with paliperidone ER as possible evidence for a signal of risk due to need to clear the capsule shell through the gastrointestinal tract. She also notes 2 cases of possible interest regarding this concern, one a ruptured duodenum and the other a GI bleed. She wants to extensively describe these cases under the standard precautionary language in labeling regarding this risk, but I disagree. The OROS formulation is well-known and has been available for years, and these minimal risks are well-known and well-characterized by the sponsor's proposed language.

5.2.3.6 Transaminase Elevations

There was no signal for mean increase in transaminase levels for the placebo-controlled trials with paliperidone. There were several outliers ($\geq$ 3XULN) in the controlled trials and in open label extensions, several of which were discontinued due to these increases. In her proposed labeling comments, Dr. Brugge notes a case of both transaminase increase and bilirubin increase, but says nothing about the case in her review. We further explored this case (CRF ID:501245) and discovered that the patient also had alkaline phosphatase elevation and was diagnosed as "cholilithiasis."

Based on these findings, Dr. Brugge has recommended routine monitoring for LFTs, i.e., q 2 weeks for the first month, then monthly, etc. I don't think there is a reasonable basis for requesting such monitoring and I won't make this recommendation.

5.2.3.7 Seizures

Dr. Brugge wants to modify the sponsor's proposed labeling language for seizures. They had pooled data from the 4 placebo-controlled 6-week studies, which yield similar risks of seizure in drug and placebo patients. She wants to focus only on the 3 adult studies, which eliminates the placebo patient. She also wants to add mention of a seizure that occurred in a long-term open extension. I have no objection to the sponsor's approach or their proposed language. The one seizure occurring in an entirely different setting is not relevant to this language.

5.2.3.8 Use in Elderly Patients

Dr. Brugge wants the labeling modified regarding dosing in the elderly out of concern that renal function may be compromised and there may be other vulnerabilities in elderly patients. Although the data accumulated in elderly patients in the development program has generally not

revealed any difference in pharmacokinetics of paliperidone in elderly patients with relatively normal renal function, nor has it revealed any consistent difference in the adverse event profile, I generally agree that caution is needed in elderly patients. Thus, I have recommended 3 mg/day as the starting dose in elderly patients. Otherwise, I think the sponsor's proposed Geriatric Use section adequately reflects the data accumulated.

5.2.3.9 Risk:Benefit vs Risperidone

Dr. Brugge argues that the sponsor needs to make a case that the risk:benefit ratio for paliperidone must be superior to that for risperidone in order to justify approval of paliperidone. There is, of course, no such provision in the law or regulations, and I disagree with this requirement.

5.2.5 Conclusions Regarding Safety of Paliperidone ER in the Treatment of Schizophrenia

I agree with Dr. Khin that the adverse event profile for paliperidone ER is quite similar to that seen for risperidone, and can be adequately characterized in labeling. The one finding of some concern is the modest increase in QTc, and I agree with the Division of Cardiorenal Products that these findings should be noted in Warnings.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would adversely affect conclusions about the safety of paliperidone ER in the treatment of schizophrenia.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, paliperidone ER is not approved anywhere at this time for the treatment of schizophrenia.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted, we decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 sites, and data from these sites were deemed to be acceptable.

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have included an extensively modified version of labeling with the approvable letter.

10.2 Foreign Labeling

Paliperidone ER is not approved anywhere at this time for the treatment of schizophrenia.

10.3 Approvable Letter

The approvable letter includes our proposed labeling and requests for phase 4 commitments.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that J&J has submitted sufficient data to support the conclusion that paliperidone ER is effective and acceptably safe in the treatment of schizophrenia. However, before we can take an approval action, the sponsor needs to respond to various requests we have made and we need to reach agreement on labeling. Thus, I recommend that we issue the attached approvable letter along with our proposal for labeling, in anticipation of final approval.

cc:
Orig NDA 21-999
ODE-I/RTemple
HFD-130
HFD-130/TLaughren/MMathis/NKhin/KBrugge/KKiedrow/SHardeman

DOC: Paliperidone_Laughren_AE_Memo.doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
9/22/2006 08:32:03 AM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: NDA Review

NDA	# 21,999 (N000)
Brand Name	[redacted]
Generic Name	Paliperidone
Sponsor	Johnson & Johnson
Indication	Treatment of schizophrenia
Dosage Form	Oral (capsules)
Therapeutic Dose	3-12 mg once daily
Duration of Therapeutic Use	Chronic
Review Classification	Standard NDA Review
Date Consult Received	August 8, 2006
Date Consult Due	September 1, 2006
Clinical Division	Division of Psychiatry Products
PDUFA Date	September 30, 2006

1.0 RECOMMENDATIONS

2.0 ANSWERS TO REVIEW TEAM QUESTIONS

2.1 **Is Study SCH-1009 an adequate basis for estimating the QT effects of paliperidone?**

2.1.1 **Response:** Yes. Study SCH-1009 is an adequate basis for estimating the QT effects of paliperidone.

2.2 **Are the QT data from study SCH-1009, along with the QT findings from the phase 3 clinical studies with paliperidone, a sufficient basis for concluding that paliperidone ER, at the doses recommended, is adequately safe?**

2.2.1 **Response:** The QT data are consistent with a QT signal for paliperidone. While the sponsor has claimed that the peak plasma concentrations at steady-state with 8 mg IR paliperidone (mean 113 ng/ml) were more than twice as high as that achieved by the highest dose of ER OROS paliperidone (12 mg: mean 45 ng/ml), the clinical pharmacology reviewer has found that concentrations achieved in the QT study (given the variability) appear to overlap with clinical doses. The extent of the signal in the QT study suggests that a low QT risk is present.

2.3 **Is there any need for additional QT data before reaching a conclusion about the cardiovascular safety of paliperidone ER?**

2.3.1 **Response:** We would have liked to verify that the QT measurements were made appropriately. In order to do this, we ask that the sponsor submit the ECGs to the ECG warehouse.

2.4 **Is the roughly 50% increase in paliperidone ER Cmax with food a cause for concern regarding the cardiovascular safety of paliperidone?**

2.4.1 **Response:** Given the known food effect, the labeling should specify that the drug should be administered without food.

2.5 **Does the proposed labeling for paliperidone ER adequately reflect the cardiovascular risks associated with this drug?**

2.5.1 **Response:** No. In fact, we do not agree with the description of study results in the proposed labeling. Please see Section 6.0 of this review for a more detailed discussion of the proposed labeling.

2.0 GOAL OF THE REVIEW

The purpose of this review is to provide input and recommendations about QT findings for paliperidone based on study SCH-1009

3.0 BACKGROUND

3.1. Indication: Paliperidone ER is being proposed for the treatment of schizophrenia.

3.2. Drug Class: Paliperidone is a major active metabolite of risperidone, which is approved in the treatment of schizophrenia. Both risperidone and paliperidone are centrally active dopamine D2 and 5-HT_{2A} antagonists.

3.3. Regulatory Classification: NDA # 21-999 for paliperidone is currently under review in the Division of Psychiatry Products.

3.4. Market approval status

Paliperidone is not approved for use for any indication in the United States. However, risperidone has been available in the US for over 10 years.

3.5. Clinical Pharmacology

According to the protocol, the Tmax of IR paliperidone is 2.0 + 1.1 hours with a terminal half-life of about 1 day.

4.0. SPONSOR'S SUBMISSION

4.1. Thorough QT study

4.1.1. Synopsis

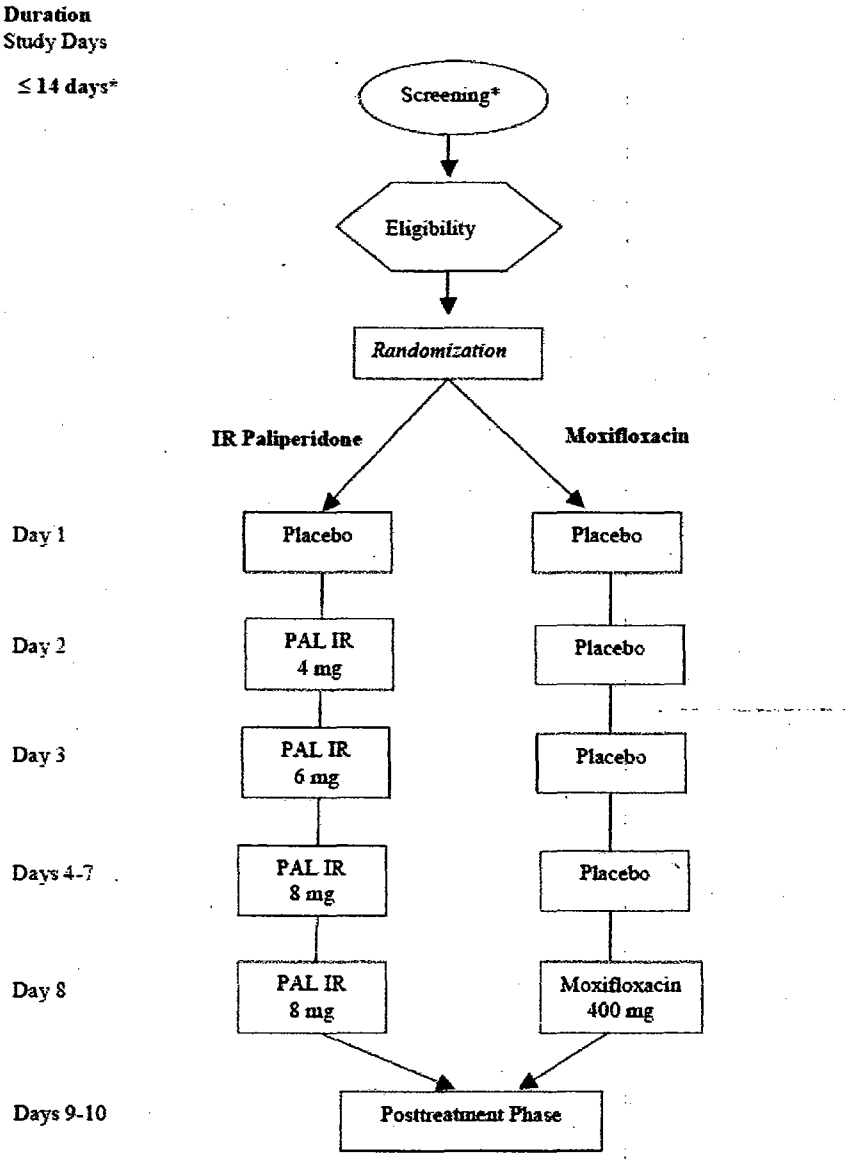
4.1.1.1. Title: A Placebo- and Positive-Controlled, Randomized Study Evaluating QT and QTc Intervals Following Administration of Immediate-Release Paliperidone in Subjects with Schizophrenia or Schizoaffective Disorder (Feb. 2-May 26, 2005)

4.1.1.2. Protocol Number: RO76477-SCH-1009

4.1.1.3. Primary Objective: To assess the cardiovascular safety of paliperiodne in schizophrenic or schizoaffective patients, with particular attention to the length of the QT/QTc interval.

4.1.2. Design: This was a randomized, double-blind, placebo and active-controlled study in patients with schizophrenia or schizoaffective disorder. The IR formulation of paliperidone was utilized in this study. A diagram of the study design is shown below:

Figure 1: Study Design for Protocol R076477-SCH-1009



* Included a 5-day washout period (Days -5 to -1) during which all prestudy medications were discontinued.

4.1.2.1. Justification for design provided: The sponsor did not provide a justification of the study design (other than justifying single-dose moxifloxacin).

4.1.3. Population: Patients with schizophrenia and schizoaffective disorder, aged 18-50 years, with normal screening 12-lead ECG. Patients with electrolyte disorders, risk factors for torsades de pointes, and significant cardiovascular history were excluded from the study.

4.1.3.1. Justification for dose provided: The dosage of 8 mg/day IR paliperidone was expected to provide plasma concentrations higher than those associated with the highest dosage (150 mg-equivalent Q 4 weeks) being considered for use in the paliperidone palmitate program. The IR formulation was chosen because of more predictable plasma concentrations and a shorter time to steady state, and the expectation that the IR dosage would cover the entire concentration range for the highest planned dosages of bother formulations in current clinical development.

4.1.4. Study Schedule and Timing of Samples

Study Day	**0**	**1, 2, 3, 4**	**5-7**	**8**	**9-10**
Intervention	No treatment	Dosing	Dosing	Dosing	Posttreatment
12-Lead ECGs	Record ECGs### (Baseline)	Record ECGs###	Single ECG pre-dose only	Record ECGs###	Record ECGs #
PK Samples for drug	None collected	Collected###	Pre-dose only	Collected###	Collected *
Meal Instructions	1 hour before first ECG	1 hour before 1st ECG	Not stated	1 hour before 1st ECG	1 hour before 1st ECG

###0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 12 hours post dose
#Day 9: 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 30 and 36 hours after the Day 8 dose.
Day 10: 48, 48.5, 49, 49.5, 50, 50.5, 51, 51.5, 52, 54, and 60 hours after the Day 8 dose.
* 24, 36, 48 and 60 hours after the Day 8 dose.

4.1.5. QT Measurement: Standard 12-Lead ECGs were obtained while subjects were recumbent. ECGs were read centrally; readers were blinded to time and treatment. The QT was calculated from lead 2.
The primary correction method was QTcLD, calculated with linear regression technique.

4.1.6. Controls: The Sponsor used both placebo and positive (moxifloxacin) controls.

4.1.7. Blinding: Paliperidone, over-encapsulated moxifloxacin (to match paliperidone) and placebo were identical in appearance in order to preserve blinding.

4.1.8. Baseline: The Sponsor planned to collect time-matched baseline QTc values on the day prior to initiating dosing (Day -1) of the study for each treatment.

4.1.9. Endpoints: The primary evaluation was based on individual linear correction method, calculated with linear regression.
4.1.10. Safety assessments: adverse events, laboratory tests, and vital signs.

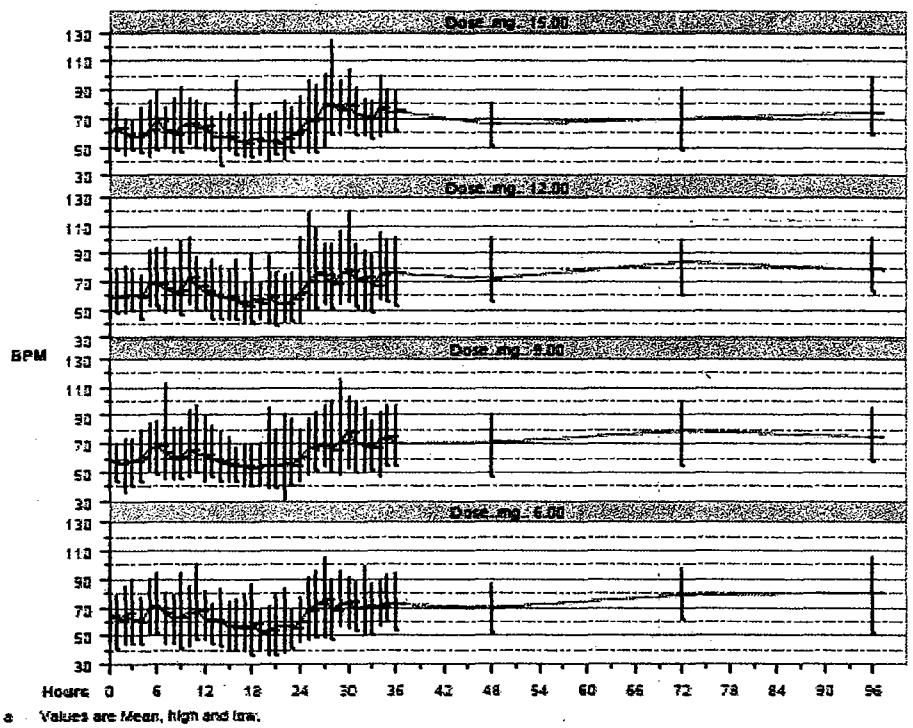
4.1.11. Results
Patient Disposition: A total of 141 patients were randomized to IR paliperidone 8 mg (n=72) or moxifloxacin 400 mg (n=69). All 141 patients were included in the safety

analysis set. The pharmacodynamic analysis set included 44 paliperidone and 58 moxifloxacin patients who received at least 1 dose of study medication and completed the ECG assessments on Days 9 and 10; eight subjects were excluded due to significant protocol deviations. Twenty-four patients discontinued prematurely from paliperidone (8 due to adverse events (AE) and 8 patients discontinued prematurely from moxifloxacin (1 due to AE).

Baseline characteristics: The safety analysis population was 79% male and 55% Black; the mean age was 39 years.

Effect on Heart Rate:
From the graph below, there appears to be little or no effect on heart rate.

Figure 78 Effect of Single Doses of Paliperidone OROS on Heart Rate over Time by Dosage Heart Rate – Study Alza-044[a]



a Values are Mean, High and low.

(Source: OCPB Review: Dr. Kavanagh)

12-lead ECGs: No ECGs were submitted to the ECG warehouse. Therefore, this reviewer is unable to verify that the QT measurements were appropriate.

Analysis of Central Tendency:
The primary ECG variable was the difference in day-averaged QTcLD between IR paliperidone 8 mg at steady state (Day 8) and placebo (Day 1). This analysis produced the following result (below):

Table 12: Day-Averaged QTcLD: Least Square Mean Differences From Day 1
(Study R076477-SCH-1009: Pharmacodynamic Analysis Set)

Treatment Arm	Visit	Treatment Group	LSMean (SE)	LSMean Difference (SE)	90% CI on LSMean Difference[a,b]
IR Paliperidone (N=44)	Day 1	Placebo	387.6 (2.22)		
	Day 2	4 mg IR q.d.	390.6 (2.23)	3.0 (1.10)	(1.18; 4.79)
	Day 3	6 mg IR q.d.	388.1 (2.22)	0.6 (1.09)	(-1.23; 2.36)
	Day 4	8 mg IR q.d.	390.5 (2.23)	2.9 (1.10)	(1.13; 4.75)
	Day 8	8 mg IR q.d.	393.0 (2.22)	5.5 (1.09)	(3.66; 7.25)
	Day 9	Posttreatment	390.5 (2.22)	3.0 (1.09)	(1.18; 4.77)
	Day 10	Posttreatment	389.8 (2.22)	2.2 (1.09)	(0.45; 4.05)
Moxifloxacin (N=58)	Day 1	Placebo	391.8 (1.87)		
	Day 2	Placebo	391.8 (1.87)	-0.0 (0.84)	(-1.40; 1.36)
	Day 3	Placebo	390.6 (1.87)	-1.2 (0.84)	(-2.59; 0.17)
	Day 4	Placebo	391.1 (1.87)	-0.7 (0.84)	(-2.09; 0.67)
	Day 8	400 mg q.d.	396.1 (1.87)	4.3 (0.84)	(2.88; 5.64)
	Day 9	Posttreatment	393.1 (1.87)	1.3 (0.84)	(-0.10; 2.65)
	Day 10	Posttreatment	390.8 (1.87)	-1.0 (0.84)	(-2.38; 0.38)

[a] The 2-sided 90% confidence intervals around the mean difference in day-averaged QTcLD during and after paliperidone treatment compared with day-averaged QTcLD on during placebo treatment (Day 1) was constructed using the estimated least-squares means and variances from the mixed models with treatment as a fixed effect and subject as a random effect.

[b] The mean effect of IR paliperidone 8 mg at steady-state (Day 8) on QTc-interval was considered "negative" if the 2-sided 90% confidence interval excluded 10 ms. Assay sensitivity was confirmed, i.e., moxifloxacin 400 mg had a positive effect on QTc interval if the 2-sided 90% confidence interval excluded 0 ms.

It will be noted that LSM Differences from Day 1 for both paliperidone and moxifloxacin were low. However, the day-averaged analysis does not take into account the time course of effect or effects at peak concentrations of drug.

An analysis of LSM Change from baseline in QTcLD by time post-dose yielded the following results:

Table 80 Least Squates Mean Change from Baseline ± SE and (90% CI) in QTcLD by Time Post-Dose – Study SCH-1009

Time Postdose	Day 2	Day 3	Day 4	Day 8	
	PAL 4 mg	PAL 6 mg	PAL 8 mg	PAL 8 mg	Moxi 400 mg
n	44	44	44	44	58
Predose	0.70 ± 1.66 (-2.00 - 3.45)	0.40 ± 1.66 (-2.36 - 3.11)	1.00 ± 1.66 (-1.77 - 3.68)	2.50 ± 1.66 (-0.27 - 5.18)	-1.1 ± 1.5 (-3.55 – 1.39)
0.5 h	4.70 ± 1.66 (2.02 - 7.46)	2.80 ± 1.65 (0.07 - 5.49)	5.50 ± 1.65 (2.75 - 8.17)	6.90 ± 1.65 (4.21 - 9.62)	3.3 ± 1.49 (0.83 – 5.72)
1.0 h	4.90 ± 1.64 (2.22 - 7.60)	4.30 ± 1.64 (1.58 - 6.96)	5.60 ± 1.64 (2.90 - 8.28)	8.10 ± 1.64 (5.40 - 10.78)	1.8 ± 1.49 (-0.69 - 4.21)
1.5 h	9.30 ± 1.65 (6.56 - 11.98)	6.70 ± 1.64 (4.04 - 9.42)	9.60 ± 1.64 (6.92 - 12.31)	10.90 ± 1.64 (8.24 - 13.62)	3.7 ± 1.49 (1.24 -6.16)
2.0 h	5.50 ± 1.65 (2.76 - 8.18)	4.60 ± 1.64 (1.94 - 7.33)	7.30 ± 1.64 (4.56 - 9.94)	8.90 ± 1.64 (6.22 - 11.60)	3.5 ± 1.49 (1.05 - 5.95)
2.5 h	3.40 ± 1.64 (0.67 - 6.06)	4.00 ± 1.64 (1.35 - 6.74)	4.70 ± 1.65 (1.98 - 7.40)	7.50 ± 1.65 (4.83 - 10.24)	5.5 ± 1.49 (3.05 – 7.97)
3.0 h	4.00 ± 1.64 (1.33 - 6.71)	2.80 ± 1.64 (0.10 - 5.49)	7.20 ± 1.66 (4.52 - 9.97)	7.70 ± 1.64 (4.99 - 10.37)	6.1 ± 1.49 (3.64 – 8.53)
3.5 h	3.40 ± 1.64 (0.74 - 6.12)	-0.10 ± 1.64 (-2.83 - 2.56)	3.70 ± 1.65 (0.95 - 6.37)	5.00 ± 1.64 (2.29 - 7.67)	4.7 ± 1.49 (2.26 -7.18)
4.0 h	2.90 ± 1.64 (0.22 - 5.60)	2.00 ± 1.64 (-0.65 - 4.74)	3.20 ± 1.65 (0.52 - 5.93)	5.80 ± 1.64 (3.06 - 8.44)	5.7 ± 1.5 (3.25 – 8.19)
6.0 h	2.00 ± 1.64 (-0.74 - 4.65)	-1.30 ± 1.64 (-3.94 - 1.44)	1.30 ± 1.64 (-1.37 - 4.01)	4.80 ± 1.64 (2.08 - 7.46)	5.0 ± 1.49 (2.57 – 7.47)
12.0 h	1.80 ± 1.65 (-0.86 - 4.55)	-1.10 ± 1.66 (-3.82 - 1.63)	1.30 ± 1.65 (-1.45 - 3.96)	3.60 ± 1.65 (0.93 - 6.35)	3.5 ± 1.5 (1.07 – 6.01)

(Source: OCPB Review: Dr. Kavanagh)

It can be seen that at peak concentrations, the upper bound of the 90% CI crosses 10 msec for paliperidone IR (all doses and Study Days).

- A concern was raised about the study design: since Day 1 is placebo for both groups, the investigator will know that Day 1 is placebo and, therefore, the study will not be "double-blind" (perhaps single-blind) for Day 1. However, this premise is not fundamentally different from a "no-treatment" baseline.

- A more straighforward design would have been a three-arm parallel study, using paliperidone, placebo and moxifloxacin arms.

- We analyzed the data, considering Day 1 as the baseline measurements and we compared the baseline adjusted QT effect of the drug to the corresponding baseline adjusted QT intervals of placebo in the positive control arm; i.e., PAL IR 4 mg (6 mg, 8 mg) with Day 2 (Day 3, Days 4-7) placebo in the moxifloxacin arm. We realize that this analysis might yield inconsistence results between the drug-placebo comparison and the moxifloxacin-placebo comparison since it is a two group comparison for the drug and placebo and one group comparison for the moxifloxacin and placebo; however, at least our results are based on a double-blinded design.

- Our results for the drug at Day 8 are provided in the following Table 1. As can be seen from this table, at multiple time points, the one-sided 95% upper confidence intervals are above 10 msec, which have already demonstrated assay sensitivity of the study. The upper bound crosses the threshold of regulatory concern and is consistent with results from the clinical pharmacology review.

Table 1 The mean difference of double delta of the drug and placebo at Day 8

Time	# of Subj. PALI D8	Mean Delta QTcF PALI D8	# of Subj. Placebo D4	Mean Delta QTcF Placebo D4	Double Delta	SD	95%CI LOW	95%CI HIGH
0	49	3.31	59	0.27	3.04	2.12	-0.45	6.53
0.5	50	6.32	61	-0.28	6.6	2.63	2.27	10.93
1	51	7.94	61	-2.36	10.3	2.1	6.85	13.75
1.5	50	10.02	59	-2.46	12.48	2.21	8.85	16.11
2	50	9.2	61	-2.75	11.95	1.84	8.92	14.98
2.5	49	7.49	60	-2.83	10.32	2.23	6.66	13.98
3	49	7.22	61	-0.28	7.5	2.03	4.15	10.85
3.5	49	4.57	60	-1.2	5.77	2.34	1.91	9.63
4	49	5.1	59	-1.71	6.81	1.82	3.82	9.8
6	49	5.96	60	0.32	5.64	1.92	2.48	8.8
12	48	3.35	59	-0.8	4.15	1.98	0.89	7.41

- The results of double delta analysis for moxifloxacin are provided in Table 2. At 2.5 hour after dosing, the lower bound is greater than 5 msec, which indicates that at least at one time point, the mean difference of baseline adjusted moxifloxacin and baseline adjusted placebo is at least 5 msec. The assay sensitivity was demonstrated by moxifloxacin's QTcF effect. We should point out though we did not adjust for α when comparing multiple time points for moxifloxacin. If we perform some α adjustment scheme, for instance, using the most conservative Bonferroni adjustment, the lower bound at 2.5 hour for moxifloxacin will be less than 5 msec. Note that since the drug itself also demonstrated QT prolongation

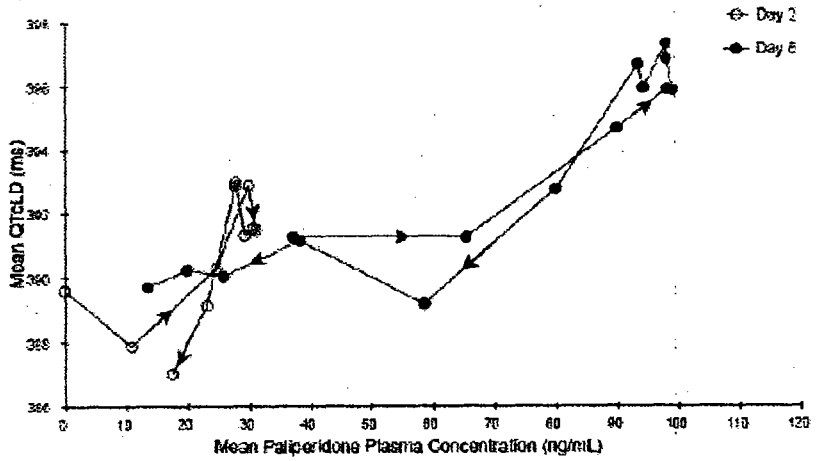
(producing even stronger signal than that from moxifloxacin), the role of moxifloxacin in this study seems not that important.

Table 2 Then mean difference of double delta of moxifloxacin and placebo

Time	# of Subj. Moxi D8	Mean Delta QTcF Moxi D8	Mean Delta QTcF Placebo D4	SD of Delta QTcF Placebo D4	Double Delta	SD	95%CI LOW	95%CI HIGH
0	59	-0.8	0.27	11.8	-1.07	1.05	-2.79	0.65
0.5	61	3.56	-0.28	16.4	3.84	1.8	0.87	6.8
1	61	1.52	-2.36	11.7	3.89	1.52	1.38	6.39
1.5	60	3.78	-2.46	11.46	5.66	1.57	3.09	8.24
2	61	3.56	-2.75	10.42	6.31	1.27	4.23	8.39
2.5	60	5.82	-2.83	13.87	8.65	1.6	6.02	11.28
3	61	6.39	-0.28	10.17	6.67	1.17	4.75	8.59
3.5	60	4.83	-1.2	10.41	6.03	1.79	3.09	8.98
4	59	6.08	-1.71	8.92	7.8	1.42	5.46	10.14
6	61	5.87	0.32	8.45	5.92	1.42	3.58	8.26
12	59	3.58	-0.8	10.35	4.88	1.18	2.93	6.83

A hysteresis plot of mean QTcLD vs. mean paliperidone plasma concentrations suggested a concentration-QTc relationship as well as a lack of hysteresis.

Figure 70 Hysteresis Plots of Mean QTcLD versus Mean Paliperidone Plasma Concentration – Study SCH-1009



(Source: OCPB Review: Dr. Kavanagh)

It should be noted that the QT study was performed with the IR formulation, which has been associated with higher exposures than the proposed marketed formulation (OROS).

According to the clinical pharmacology reviewer (Dr. Kavanagh), there appears to be "overlap of the concentrations associated with QT effect in the controlled QT study and the peak concentrations likely to be seen with clinical dosing of the OROS formulation, even without accounting for the elderly who have slightly higher peak concentrations and patients with organ dysfunction that might result in higher exposures than is typical."

Outlier Analysis:

Table 15: Number of Subjects With a Maximum Change in QTc Interval of 30 to 60 ms or ≥60 ms
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)			Placebo/Moxifloxacin (N=69)		
	Total	QTc Interval ↑ (ms)		Total	QTc Interval ↑ (ms)	
Parameter	n (%)	30-60	>60	n (%)	30-60	>60
QTcLD	19 (26)	19	0	12 (17)	12	0
QTcF	19 (26)	19	0	11 (16)	11	1
QTlc	20 (28)	20	0	13 (19)	13	0
QTcB	59 (82)	59	1	26 (38)	26	0

Number of subjects with a maximum increase in QTc of 30-60 ms or >60 ms at any time during the study relative to time-matched QTc intervals on Day 1 (placebo).

Cross-reference: Attachment 3.4.

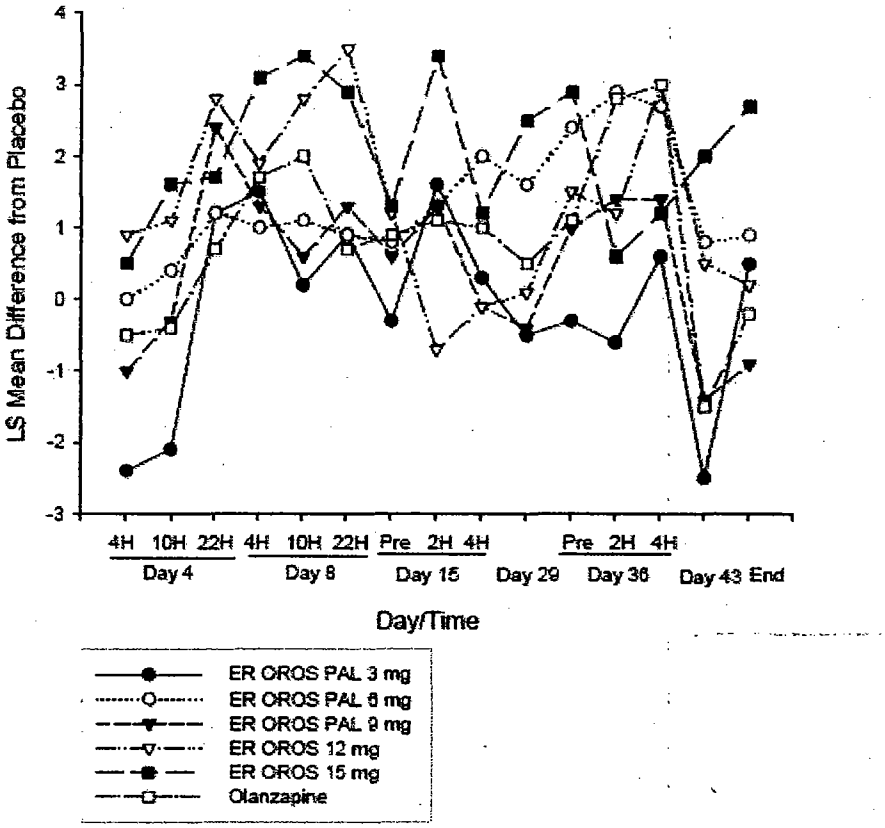
Table 17: Number of Subjects With Absolute QTc Prolongation ≥450 ms, ≥480 ms, or >500 ms
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)					Placebo/Moxifloxacin (N=69)				
		Maximum QTc Interval (ms)					Maximum QTc Interval (ms)			
	n	Normal	≥450	≥480	>500	n	Normal	≥450	≥480	>500
QTcLD	72	72	0	0	0	69	69	0	0	0
QTcF	72	72	0	0	0	69	69	0	0	0
QTlc	72	72	0	0	0	69	69	0	0	0
QTcB	72	63	8	1	0	69	63	6	0	0

4.2. Phase 3 Studies:

In the safety review, the sponsor analyzed means and mean changes in QTc over time for double-blind studies R076477-SCH-303, R0767477-SCH-304, and R076477-SCH-305 (Double-blind studies analysis set). In this analysis set, 12-lead ECGs were recorded at screening and baseline; on Days 4 (4, 10, 22 hours post-dosing), 8 (4, 10, 22 hours post-dose), 15 (pre-dose and 2, 4 hours post-dose), 29, 36 (pre-dose and 2, 4 hours post-dose), and 43 (or at endpoint) and at the poststudy visit (Day 50). According to the sponsor, the LSM differences from placebo were small (< 4 msec).

Figure 9: Least-Square Mean Difference (Treatment - Placebo) for QTcLD
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)



Note: LS Mean difference is based on the ANCOVA model with factors for treatment, baseline (average predose), study, analysis center (nested within study).

Reviewer Comment: While the sponsor's analysis did not result in a signal, this analysis did not include a measurement of assay sensitivity. In addition, we are unable to verify that the QT measurements were made appropriately.

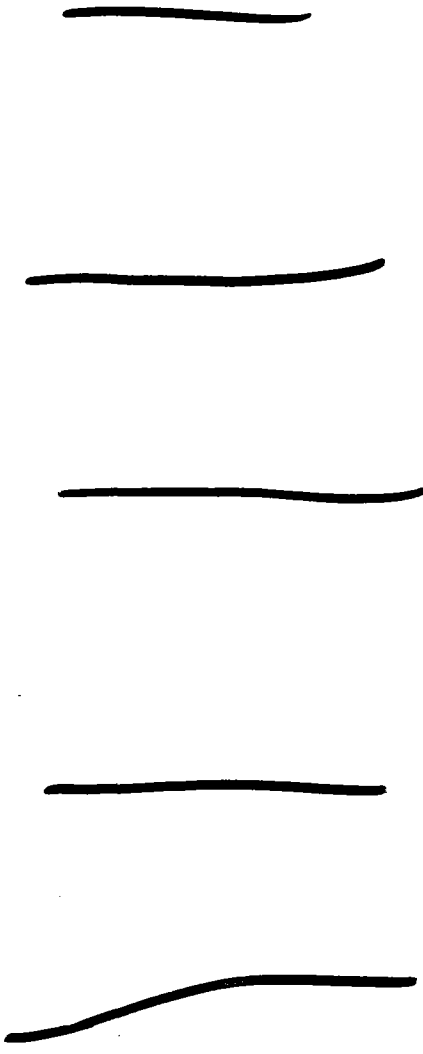
5.0. REVIEWERS' ASSESSMENT

- The QTcLC effects at peak concentration, which cross the upper bound of 10 msec, as well as the hysteresis plot for the mean change in QTcLD vs. plasma concentration, are consistent with a QT signal.
- The sponsor has claimed that peak steady-state concentrations of 8 mg IR paliperidone are more than twice the concentrations of the highest dose of OROS 15 mg paliperidone. However, the clinical pharmacology reviewer has concluded that overlap is present between concentrations in the QT study and concentrations seen with the OROS formulation.
- We conclude that, based on the available information, that a QT signal is present, although the risk for a torsade de pointes event is probably low in the targeted

range. However, labeling should include safety information in order to limit patient exposure (see below, Section 6.0).

6.0. PROPOSED LABELING: The proposed labeling includes the following: Under Clinical Pharmacology:

Electrophysiology



6.1. Reviewer Comments/Labeling Recommendations:

We do not agree with the above labeling. The sponsor's day-averaged correction does not fairly portray QTc effects at peak concentrations. Instead, QTc effects at peak concentrations should be included. For the three fixed-dose efficacy studies, the sponsor did not include a demonstration of assay sensitivity; we do not know if those studies were able to detect a positive signal.

Our best assessment, given the available information, is that there is a low QT risk. Therefore, we recommend that the following cautionary information be included in labeling:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shari Targum
9/12/2006 05:53:49 PM
MEDICAL OFFICER

Joanne Zhang
9/13/2006 09:31:26 AM
BIOMETRICS

Norman Stockbridge
9/13/2006 11:04:21 AM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 25, 2006

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 21-999 (This overview should be filed with the 11-30-2005 original submission.)

SUBJECT: Recommendation of Approvable Action for Paliperidone Extended Release OROS Oral Tablets for the Treatment of Schizophrenia

1. BACKGROUND

Paliperidone is a major active metabolite of risperidone which is an atypical antipsychotic agent approved in the treatment of schizophrenia. Both risperidone and paliperidone are centrally active dopamine D2 and 5-HT_{2A} antagonists. The proposed dose range in schizophrenia is 3 to 12 mg once daily.

IND 65,850 for paliperidone OROS was originally submitted on September 25, 2002. Several meetings were held at EOP2 with the sponsor for preclinical, CMC, OCP and clinical issues (4/25/2003, 6/20/2003, 12/12/2003). The discussions included:

- preclinical program requirements on genotoxicity data
- description of the relationship between paliperidone exposure achieved with OROS paliperidone administration compared to paliperidone exposure achieved with risperidone
- adequacy of cardiovascular safety monitoring plan including conducting a specific ECG study
- requirement for an NDA.

A pre-NDA meeting was held with the sponsor on 3/23/2005. The meeting focused on the format and contents of the NDA.

The sponsor submitted the above referenced NDA on November 30, 2005. This NDA has been reviewed by Fanghui Kong, Ph.D., from the Office of Biostatistics (review dated 08/08/2006), and Karen Brugge, M.D., Medical Officer, DPP (review dated 07/23/06; 8/18/06). The CMC reviewer for this NDA is Chhagan Tele Ph.D. The Office of Clinical Pharmacology (OCP) reviewer is Ron Kavanaugh, Ph.D. The pharmacology/toxicology reviewer is Elzbieta Chalecka-Franaszek, Ph.D. At the time of completion of this memo, the Chemistry, the pharmacology/ toxicology and the clinical pharmacology reviews are not finalized.

2.0 CHEMISTRY

I am not aware of any CMC concerns that would preclude an approvable action on this NDA.

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology issues that would preclude an approvable action for this NDA.

4.0 CLINICAL PHARMACOLOGY

I am not aware of any clinical pharmacology concerns that would preclude an approvable action for this NDA.

Paliperidone has an elimination half-life of approximately 23 hours. Steady state is reached 4-5 days. The Cmax and AUC values were increased by 42% and 46%, respectively, in the fed state compared with administration of paliperidone under fasting condition. The plasma protein binding of paliperidone is 74%. Cytochrome P450 isozymes (CYP2D6 and CYP3A4) seem to be involved in metabolism of paliperidone. In-vitro studies in human liver microsomes showed that paliperidone does not substantially inhibit the drugs metabolized by Cytochrome P450 isozymes. The pharmacokinetics does not appear to be affected by age, race, gender, smoking status or hepatic impairment. The elimination half-life of paliperidone is prolonged (41-50 hrs) in subjects with impaired renal function.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 4 short-term, double-blind, placebo-controlled trials in patients with schizophrenia. Three studies (R076477-SCH-303, R076477-SCH-304, R076477-SCH-305) were the 6-week, double-blind, placebo and active controlled (Olanzapine 10 mg), parallel-group, fixed-dose studies designed to evaluate the efficacy and safety of paliperidone ER. The doses of paliperidone ER used were 6, 9, and 12 mg in study 303; 6 and 12 mg in study 304; and 3, 9, and 15 mg in study 305. Study R076477-SCH-302 was a 6-week, double-blind, placebo controlled, flexible dose of paliperidone ER in elderly patients with schizophrenia.

The sponsor indicated that results of the 3 pivotal clinical studies, either considered individually or pooled, demonstrated that all doses of paliperidone ER OROS tested were superior to placebo on the primary efficacy variable. The sponsor also indicated that paliperidone ER did not differ from olanzapine in a pooled analysis of the 3 phase 3 fixed dose studies in adults and the results from olanzapine group was used for assay sensitivity analysis.

I would briefly describe the results of each of these paliperidone studies pertinent to efficacy claim in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

Study R076477-SCH-303

This was a randomized, double-blind, placebo and active controlled, parallel-group, 6-week, fixed-dose study comparing paliperidone ER (at fixed doses of 6, 9, 12 mg/day, given on a qd basis in the morning), olanzpine (at a fixed dose of 10 mg, given on a qd basis in the morning), and placebo. The study was conducted at 53 centers in 11 countries (Eastern and Western European; Asia) in adult (age 18 or older) patients meeting DSM-IV criteria for schizophrenia. All subjects were hospitalized for the first 14 days of double-blind treatment. The total number of subjects enrolled in this study was 628 in which 374 subjects in paliperidone treatment group. The ITT samples for paliperidone (6, 9, 12 mg), olanzapine and placebo were 123, 122, 129, 128 and 126, respectively. The subjects enrolled were mostly white, mean age was 37 yrs, and had approximately an equal distribution of male and female subjects. There seemed to be no significant differences in demographic characteristics among the treatment group. A total of 415 subjects (66%) completed the study. The number of subjects who discontinued from the study for were 35%, 30%, 22%, 30% and 54%, in paliperidone (6, 9, 12 mg), olanzapine and placebo group, respectively. The most common reason for early withdrawal was lack of efficacy.

The efficacy assessment included the PANSS and the CGI-S, administered weekly. The primary end point phase was the change in the total score of the PANSS from baseline to the last post-randomization assessment in the double-blind treatment period. The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with Dunnett's procedure to adjust for multiple doses. Dr. Kong confirmed the primary efficacy results. He also applied MMRM as a sensitivity analysis. The results are as follows:

Efficacy Results on PANSS Total Scores for Study 303 (LOCF):

	Mean Baseline PANSS (SD)	Change from Baseline Mean (SD)	P-values (vs. placebo)
Paliperidone ER OROS 6mg	94.3 (10.48)	-17.9 (22.23)	<0.001
Paliperidone ER OROS 9mg	93.2 (11.9)	-17.2 (20.23)	<0.001
Paliperidone ER OROS 12mg	94.6 (10.98)	-23.3 (20.12)	<0.001
Placebo	94.1 (10.74)	-4.1 (23.16)	

There does not seem to have an advantage of the 9 mg over 6 mg dose. However, the sponsor states that a statistically significant difference in mean change was seen between the paliperidone 12 mg and the other 2 doses 6 and 9 mg, p-values of 0.046 and 0.037, respectively.

Comment:

Both Drs. Brugge and Kong considered this a positive study for paliperidone, and I agree with them.

Study R076477-SCH-304

This was a randomized, double-blind, placebo and active controlled (olanzapine 10mg), parallel-group, 6-week, fixed-dose study comparing paliperidone ER (at fixed doses of 6, 12 mg/day, given on a qd basis in the morning), olanzpine (at a fixed dose of 10 mg, given on a qd basis in the morning), and placebo. The study was conducted at 45 centers in the U.S. in adult (age 18 or older) patients meeting DSM-IV criteria for schizophrenia. All subjects were hospitalized for the first 14 days of double-blind treatment. The total number of subjects enrolled in this study was 432 in which 222 subjects in paliperidone treatment group. The ITT samples for paliperidone (6, 12 mg), olanzapine and placebo were 111, 111, 105 and 105, respectively. The subjects were mostly male, slightly above 50% were black and mean age was 42 yrs. There seemed to be no significant differences in demographic characteristics among the treatment group. A total of 193 subjects (43%) completed the study. The number of subjects who discontinued from the study were 54%, 52%, 55% and 66%, in paliperidone (6, 12mg), olanzapine and placebo group, respectively. The most common reason for early withdrawal was lack of efficacy.

The efficacy assessment included the PANSS and the CGI-S, administered weekly. The primary end point was the change in the total score of the PANSS from baseline to the last post-randomization assessment in the double-blind treatment period.

The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with Dunnett's procedure to adjust for multiple doses. Dr. Kong confirmed the primary efficacy results. He also applied MMRM as a sensitivity analysis. The results are as follows:

Efficacy Results on PANSS Total Scores for Study 304 (LOCF):

	Mean Baseline PANSS (SD)	Change from Baseline Mean (SD)	P-values (vs. placebo)
Paliperidone ER OROS 6mg	92.3 (11.96)	-15.7 (18.89)	0.006
Paliperidone ER OROS 12mg	94.1 (11.42)	-17.5 (19.83)	<0.001
Placebo	93.6 (11.71)	-8.0 (21.48)	

The 12 mg dose exhibited a numerically greater mean decrease in PANSS total scores compared with the 6 mg dose, but this difference is not statistically significant.

Comment:

Both Drs. Brugge and Kong considered this a positive study for paliperidone, and I agree with them.

Study R076477-SCH-305

This was a randomized, double-blind, placebo and active controlled (olanzapine 10mg), parallel-group, 6-week, fixed-dose study comparing paliperidone ER (at fixed doses of 3, 9, 15 mg/day, given on a qd basis in the morning), olanzpine (at a fixed dose of 10 mg, given on a qd basis in the morning), and placebo. The study was conducted at 74 centers in 14 countries in North America, Eastern Europe, Asia, Isreal, Mexico and South Africa in adult (age 18 or older) patients meeting

DSM-IV criteria for schizophrenia. All subjects were hospitalized for the first 14 days of double-blind treatment. The total number of subjects enrolled in this study was 605 in which 359 subjects in paliperidone treatment group. The ITT samples for paliperidone (3, 9, 15 mg), olanzapine and placebo were 123, 123, 113, 126 and 120, respectively. The subjects were about 65-75% male, approximately 50% white and mean age was 38 yrs. There seemed to be no significant differences in demographic characteristics among the treatment group.

A total of 365 subjects (59%) completed the study. The number of subjects who discontinued from the study were 45%, 38%, 29%, 31% and 62%, in paliperidone (3, 9, 15 mg), olanzapine and placebo group, respectively. The most common reason for early withdrawal was lack of efficacy.

The efficacy assessment included the PANSS and the CGI-S, administered weekly. The primary end point phase was the change in the total score of the PANSS from baseline to the last post-randomization assessment in the double-blind treatment period.

The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with Dunnett's procedure to adjust for multiple doses. Dr. Kong confirmed the primary efficacy results. He also applied MMRM as a sensitivity analysis. The results are as follows:

Efficacy Results on PANSS Total Scores for Study 305 (LOCF):

	Mean Baseline PANSS (SD)	Change from Baseline Mean (SD)	P-values (vs. placebo)
Paliperidone ER OROS 3mg	91.6 (12.66)	-15.0 (19.61)	<0.001
Paliperidone ER OROS 9mg	93.9 (11.9)	-17.2 (20.23)	<0.001
Paliperidone ER OROS 15mg	94.6 (10.98)	-23.3 (20.12)	<0.001
Placebo	94.1 (10.74)	-4.1 (23.16)	

A statistically significant difference in mean change was seen between the paliperidone 3 mg and the 15 mg group (p=0.021); a numerical difference was observed between the 9 and the 15 mg groups, with a trend in p=0.074.

Comment:

I agreed with both Drs. Brugge and Kong that this study be considered a positive study for paliperidone.

Study R076477-SCH-302

This was a 6-week, double-blind, placebo controlled, multicenter study using flexible dose (3 to 12 mg/day) of paliperidone ER in elderly with schizophrenia. A total of 114 subjects were enrolled in this study; 76 subjects in paliperidone group and 38 subjects in placebo group. The study population was predominantly female (73%); mean age was 69.7 yrs (range 64-81 yrs). The results showed a trend for greater improvement based on the PANSS scores.

Because the study was intended mainly for the safety and tolerability of the paliperidone in elderly patients and was comprised of a small sample size, Dr. Kong did not include this study in his efficacy analysis. I agree with Dr. Brugge's conclusion that the result are difficult to interpret due to the small sample size in this study.

5.1.3 Comments on Other Important Clinical Issues

Evidence Bearing on the Dose-Response for Efficacy

All 3 positive studies involved fixed paliperidone ER doses. The doses included were: 6, 9 and 12 mg in study 303; 6 and 12 mg in study 304; and 3, 9 and 15 mg in study 305. The studies were not optimally designed to study dose-response. Dr. Brugge has recommended a target dose of 6 mg/day mainly based on the fact that there was more support for this dose than for the 3 mg dose. I would prefer targeting the 3 mg dose, with the possibility of titration. The labeling should include information regarding the demonstrated efficacy compared to adverse events profile of the drug at higher doses. It is noted that risperidone labeling provides specifications on dose adjustment in the dosing and administration section of the labeling. We should provide the same for paliperidone labeling. We should ask the sponsor to conduct a fixed dose study in this patient population to give a better understanding in the lowest effective dose, the dose titration schedule and interval. We should obtain the sponsor's commitment to conduct this as a phase IV study.

Subgroup Analyses

Exploratory subgroup analyses were done by the sponsor and the Statistical Reviewer to detect subgroup interactions on the basis of gender, age and race.

As Dr. Kong pointed out in his review, the majority of study subjects (87%) were white and over 70% of the study subjects were between age 25 and 50. Dr. Brugge noted that there was a numerical improvement on the primary efficacy variable for each paliperidone treatment group compared to placebo. Because of the small sample size, the results are difficult to interpret for these smaller subgroups.

The gender did not seem to have an effect on the significance level of the treatment on the primary efficacy endpoint, i.e, no treatment and gender interaction in all 3 studies (303, 304 and 305).

Mean effect size, as measured by difference between drug and placebo, were comparable between males and females in all these studies although the sample size, as Dr. Kong notes in his review that, was considerably larger in the male group in studies 304 and 305.

Overall, there is no clear indication of subgroup differences in response based on these variables. The effect size observed in these positive studies seemed similar to that seen in other schizophrenia trials.

Secondary Efficacy Variables

In the proposed labeling, the sponsor intends to claim efficacy evaluation using the PANSS factors and the Personal and Social Performance (PSP) scale. Although the results from these secondary efficacy measures were reported to be positive, these were not pre-specified outcome measures.

Therefore, we should not accept the sponsor's proposal to include these two variables in the labeling unless the sponsor could provide documentation that the studies were prospectively planned to include such claim.

[redacted]

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analyses of all 3 fixed-dose studies supported the efficacy claim of paliperidone ER OROS in the treatment of schizophrenia in all of the dose groups tested. The sponsor has not adequately explored the lower end of the dose response curve for paliperidone. We should obtain the sponsor's commitment to conduct a study to identify the minimal effective dose and dose titration/adjustment as a phase IV study. The issue of [redacted]

5.2 Safety Data

5.2.1 Satety Database

Dr. Brugge's safety review of this NDA was based on an integrated database covering 37 clinical trials in the drug development program for paliperidone. This included:

1) clinical pharmacology studies comprised of 27 phase 1/2a studies
   - 17 pooled trials of healthy adults
   - 3 pooled trials of schizophrenia patients
   - unpooled data from 7 other trials
2) clinical efficacy and safety phase 3 studies
   - 4 completed phase 3 double-blind studies in subjects with schizophrenia
   - 1 ongoing phase 3 double-blind relapse prevention study
   - 5 ongoing phase 3 open-label extension studies

Dr. Brugge's safety review included data from the original submission and also a 4-month safety update, with a cut-off date of 05/31/2005 (8/31/2005 for deaths and SAEs) and 11/1/2005, respectively.

The program included 592 paliperidone exposed subjects out of 1048 subjects enrolled in the clinical pharmacology trials and 1523 paliperidone exposed subjects in the phase 3 safety/efficacy trials, representing 507.59 patient-years of exposure.

The patient distribution for the sample was as follows:

- 383 subjects with schizophrenia or schizoaffective disorder in phase 1/2a studies; and
- 1039 schizophrenia patients (out of 1796 enrolled) in the 4 completed phase 3 double-blind treatment; 1167 patients then received open-label ER OROS paliperidone

- 462 schizophrenia patients had been enrolled in the ongoing phase 3 double-blind relapse prevention study (study 301)

The ICH criteria for duration of drug exposure were met for ≥6 months and ≥12 months, with n=687 exposed for ≥29 weeks and n=228 exposed for >52 weeks based on the total duration of paliperidone exposure table provided in the safety report update by the sponsor.

There were no deaths reported in the paliperidone treatment group in the phase 3 double-blind studies. Serious adverse events were available from these trials. There were no post-marketing data since paliperidone ER OROS is not marketed any country in the world.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). In the double-blind studies, the AEs of tachycardia, akathesia, and EPS occurred more frequently in subjects who received paliperidone. However, there are several AEs that, while not strictly meeting these criteria, did appear at a higher rate for paliperidone mostly at high doses vs. placebo: dystonia, hypertonia, orthostatic hypotension, headaches and hypersalivation.

5.2.2.2.1 Extrapyrimidal Symptoms

Pooled data from the three placebo-controlled, fixed dose studies also suggested evidence of treatment emergence and dose-relatedness for EPS with the higher doses of paliperidone. Compared to the EPS rate of 2.3% in placebo group, the percentage of subjects with EPS were 4.7%, 2.1%, 6.9%, 7.4% for 3 mg, 6 mg, 9 mg and 12 mg dose groups of paliperidone, respectively.

5.2.2.2.2 Akathesia

Similarly, the rate of akathesia was 3.9% in placebo group, the percentage of subjects who experienced akathesia were 3.97%, 3.0%, 8.1%, 9.5% for 3 mg, 6 mg, 9 mg and 12 mg dose groups of paliperidone, respectively.

5.2.2.2 Mortality in Elderly

Two subjects who participated in the elderly study 302 died in the course of the study. Subject 200308 died from coma due to subdural hygroma; subject 200718 died from cardiac arrest due to lung cancer. Both of these subjects were assigned to placebo. The sponsor's proposal of this topic in the paliperidone labeling that include information from the Boxed Warning and the Warning sections of risperidone labeling on increased mortality and cerebrovascular AE including stroke in elderly patients with dementia related psychosis seems reasonable.

5.2.2.3 Orthostatic Hypotension

Orthostatic hypotension was observed with greater frequency in subjects who received paliperidone ER OROS consistent with the known pharmacology of risperidone and paliperidone. Specifically, pooled data from the three placebo-controlled, fixed dose studies showed the incidence rate of orthostatic hypotension in placebo group was 0.8% while the percentage of patients who experienced orthostasis in paliperidone groups were 2.4%, 1.3%, 2.4% and 3.7%, with 3 mg, 6 mg, 9 mg and 12 mg dose, respectively.

5.2.2.4 Vital Sign Changes

As expected based on its alpha-blocking activity, ER OROS paliperidone was associated with a higher incidence of abnormally high supine and standing pulse rates compared to placebo. These findings were consistent with the higher incidence of adverse events of tachycardia in subjects who received ER OROS paliperidone versus placebo. Based on the results from the short-term, fixed-dose, placebo-controlled trials, the percentages of subjects with tachycardia were 2.4%, 7.2%, 7.3%, 7.4% with the 3, 6, 9 and 12 mg paliperidone treated group, respectively, while the rate was 2.8% in the placebo group.

A mean increase from baseline in heart rate (both standing and supine tachycardia) was observed. It was time-dependent and dose-dependent with greatest effects generally observed in the high dose group (15 mg). The mean increase observed in this group for supine heart rate was 6.8±12.9 bpm on Day 6 (ranging up to a maximum individual-subject increase of 128 bpm) compared to 0.6+11 bpm in placebo group. The 15 mg paliperidone treated group generally showed higher mean increases of standing heart rate up to 7 bpm (SD of ±14 or ±15) on Days 3 and 4 with little to no change in the placebo group (mean change of 1.5 to -0.8).

5.2.2.5 ECG and QTc Findings

ECG data were available from the three fixed-dose, placebo-controlled, phase 3 studies. ECG data were available from the phase 1/2a PK studies as well. In addition, the sponsor conducted a cardiovascular safety study (study R076477-SCH-1009).

Study R076477-SCH-1009
This was a double-blind, placebo and active controlled (moxifloxacin 400 mg), randomized study in subjects with schizophrenia or schizoaffective disorder (total N=141). Study subjects were randomized to paliperidone immediate release (IR) or the positive control, moxifloxacin, on Day 1. All subjects received a single dose of placebo on Day 1 in the paliperidone IR treatment group, and on Days 1 to 7 in the moxifloxacin treatment group. In the paliperidone IR treatment group (N=72), subjects received paliperidone 4 mg/day q.d. on Day 2, 6 mg/day q.d. on Day 3, and 8 mg/day q.d. on Days 4 through 8. In the moxifloxacin treatment group, subjects received moxifloxacin 400 mg on Day 8. Both groups were followed off treatment on Days 9 and 10.

Day-averaged QTcLD showed a LS mean difference of 5.5±1.09 ms (90% CI 3.66-7.25) at Day 8 for the paliperidone IR group and a difference of 4.3±0.84ms (90% CI 2.88-5.64) at Day 8 for the moxifloxacin 400 mg group, compared to placebo at Day 1. None of the paliperidone IR subjects showed a QTc increase of greater than 60 ms. None of the paliperidone IR subjects showed

prolonged QT values exceeding 450 ms for males and 470 ms for females except that QTcB was prolonged in 7 out of 72 paliperidone IR subjects. Paliperidone increases the heart rate be noted.

The formulation used in study SCH-1009 was the immediate release formulation of paliperidone. It should be noted further that the Cmax ss for paliperidone IR 8 mg qd is 113 ng/mL, approximately 2.5 times the Cmax ss for paliperidone ER 12 mg qd, i.e., 45 ng/mL.

I note in Dr. Brugge's review that 1 subject (201102), a 23 year old male with no cardiac history who received 12 mg paliperidone ER in study 303 was reported as an adverse dropout due to abnormal ECG (QTcF of 454 msec on Day 6).

There is a greater incidence of AV block in the 15 mg paliperidone group (4.4%) compared to placebo (1.4%). In the elderly study 302 using flexible doses of paliperidone, First degree AV block was observed in 3% (2 subjects out of 76 paliperidone) compared to no events in placebo subjects.

Recently, DPP has sent a consult to the Division of Cardiorenal Products to comment on whether study SCH-1009 is an adequate basis for estimating the QT effects of paliperidone. We are awaiting their input on the QT data from study SCH-1009, along with the QT findings from the phase 3 clinical studies with paliperidone, a sufficient basis for concluding that paliperidone ER, at the doses recommended, is adequately safe. We also asked for any need for additional QT data before reaching a conclusion about the cardiovascular safety of paliperidone ER.

5.2.2.6 Syncope

In the original submission (N000), results of the short-term phase 3 trial dataset noted that syncope was reported in 1 subject (<1%) in each treatment group of paliperidone including the placebo.

In response to the questions raised by Dr. Brugge regarding subjects with potential vital sign related events and for the safety update review, the sponsor provided an amendment submission (N007). In this amendment, the sponsor reported that a total of 49 subjects (3%) who were asymptomatic at baseline (out of 1682 subjects) in the pooled double-blind studies were identified as symptomatic during treatment (paliperidone ER OROS 3%, 32/963; placebo 2%, 7/355; olanzapine 3%, 10/364). The sponsor concluded that 12 of these 49 subjects may have confounding cause (e.g., concomitant medication or medical condition) including 7 of 32 subjects in paliperidone group, 3 of 7 placebo subjects and 2 of 10 olanzapine subjects). The sponsor also noted that the remaining subjects, there was insufficient information to draw conclusion. On this list of 49 symptomatic subjects, 10 subjects were listed to have experienced syncope: 7 subjects out of 963 in paliperidone group (0.73%); 1 subject out of 355 subjects (0.28%) in placebo group; and 2 subjects out of 364 in olanzapine group (0.55%). I acknowledge Dr. Brugge's concerns of vital sign related events. Based on these numbers of events, Dr. Brugge's recommendation that the sponsor be asked to provide more description (line listings and narratives) on cases using various vital sign cutoffs, as listed in her review, seems unnecessary at this time.

We are awaiting an input from the Cardiorenal whether they have any concerns on possible QT effect of drug, and if any, would have contributed in causing syncope.

5.2.2.7 Neuroleptic Malignant Syndrome

Neuromuscular malignant syndrome (NMS) was not reported for any subjects in the completed Phase 3 trials (-302 through -305) or for the ongoing OL studies (-701 through -705). According to the sponsor, NMS and increased blood creatine phosphokinase (CPK) were reported for 1 subject (100057) in the ongoing "prevention of recurrence" trial, Study -301 after receiving 3 weeks of blinded study drug. NMS was resolved following discontinuation of treatment. Dr. Brugge noted that, based on her review of case narratives, there may be an additional case. NMS is one of the subsections in the Warnings section of the proposed labeling. The language is similar to the risperidone labeling. It seems acceptable to me.

5.2.2.8 Tardive Dyskinesia

There were 2 reports of tardive dyskinesia (1 during the double-blind and 1 during the open-label paliperidone ER OROS treatment). It appears acceptable as the description of TD in the proposed labeling is almost identical to that of risperidone.

5.2.2.9 Abnormal Laboratory Tests

5.2.2.9.1.1 Hyperglycemia and Lipid Profiles

The sponsor reported that the effects of ER OROS paliperidone on the results of chemistry and hematology laboratory tests (including liver and renal function tests, serum lipid levels, and glucose levels) did not show clinically relevant differences from those of placebo. Hyperglycemia and diabetes mellitus is described under Precautions of risperidone and so as for some other antipsychotic drugs. The sponsor's report on hyperglycemia and diabetes mellitus in paliperidone treated subjects (1%) has not revealed any new or unexpected findings. Given the fact that paliperidone is the major metabolite of risperidone, I have no objection of the sponsor's proposal to use most of the language from risperidone in the paliperidone labeling.

5.2.2.9.1.2 Hyperprolactinemia

Dose dependent group mean increases in prolactin levels were observed with greater frequency in subjects who received paliperidone ER OROS in the phase 3 fixed dose dataset. Phase 1/2a results with schizophrenia patients revealed similar mean Prolactin level increases in Pal groups (OROS and non-OROS groups compared) to Risperidone treatment (i.e., mean levels of 32.1 and 37.0 ng/ml were observed in the high dose OROS Pal and the risperidone groups, respectively). The Agency has requested the sponsor to make revisions to the precaution section regarding hyperprolactinemia associated with risperidone. The sponsor has recently submitted a response to the risperidone NDA supplement on this issue and is under review. Given the finding that prolactin levels among paliperidone treated subjects generally is similar to those observed during treatment with risperidone, we would modify the language in paliperidone accordingly.

5.2.2.9.1.3 CPK

Dr. Brugge noted in her review that elevations in CPK levels were observed in phase 3 trials. However, she pointed out that these elevations were inconsistent across treatment groups, varied widely among subjects and showed large fluctuations over time within a given subject. There were

no other serious events associated with CPK elevations except for two cases of NMS as described before. In her review dated 8/18/06, Dr. Brugge provided her review of additional information by the sponsor on this topic including the elevated CPK levels from the phase 1 trials. She noted that if the sponsor cannot provide convincing data to explain that these elevations are not drug-related, labeling should include [redacted] She also noted that since CPK elevations can occur in acutely psychotic patients for non-drug related reasons, the highly variable CPK elevations observed in patients in the phase 3 trials are difficult to interpret.

5.2.2.10 Weight Gain

Mean body weight and BMI showed dose-related increases during double-blind treatment with ER OROS paliperidone. In the 6-week, double-blind Phase 3 trials (R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305), mean weight increases were 0.6 kg for subjects who received 3 or 6 mg/day, 1.0 kg for subjects who received 9 mg/day, and 1.1 kg for subjects who received 12 mg/day of ER OROS paliperidone. Weight increases were infrequently reported as adverse events.

5.2.2.11 Suicidality

The sponsor has provided the methodology in their effort to identify subjects with suicidality that was reported in the CRFs. In the pooled double-blind phase 3 studies, the incidence of suicide related AEs listed 7 subjects in paliperidone treatment group (N=1039), 4 subjects in the placebo group (N=355), and 5 subjects in the olanzapine treatment group (N=364). I acknowledge Dr. Brugge's comments and discussion of this topic in her assessment of quality and completeness of data. She pointed out that there was a note in the table for not including several subjects in the subject listing if the investigator reported symptom as part of overall clinical condition or investigator denied suicidality. She questioned on whether or not there should be additional search term to find existence of other uncaptured subjects. It is known that the risk of suicide is high among patients with schizophrenia and some apparent suicide may be in response to the psychotic illness (in case of command hallucinations). The sponsor's proposed language on this topic in one of subsections in the Precaution section of the labeling seems adequate at this time.

5.2.3 Additional Concern of a Food Effect

Results from the study R076477-P01-1008 showed food effects in which approximately 42-46% increase in the Cmax and AUC were observed in the fed compared to the fasted state. As pointed by Dr. Brugge in her review, food effects were observed on PK data may in turn increase in mean systolic BP (i.e., 13.5 mmHg in the fed to-be-marketed [redacted] Pal treatment condition at 36 hours postdose) that began at approximately 29 or 30 hours post-dose that was less prominent in the fasted conditions in Phase I studies. Group mean increase in heart rate to a similar extent in fasted and fed treatment conditions was also observed that occurred near the same time as the increased BP.

Risperidone and Paliperidone used mostly in PK studies were an immediate release formulation while the to-be-marketed formulation of paliperidone is an extended release oral OROS formulation which was also used in the phase 3 clinical studies stated above. It should be noted further that the Cmax ss for paliperidone IR 8 mg qd is 113 ng/mL, approximately 2.5 times the Cmax ss for paliperidone ER 12 mg qd, i.e., 45 ng/mL. Labeling will need to be clear in noting this issue. Based on my discussion with the biopharm reviewer (final review not yet available at this time), Dr.

Kavanaugh stated that the food effect is likely due to the OROS formulation and such food effect results can be addressed adequately in the labeling.

As stated before, recently, DPP has sent a consult to the Division of Cardiorenal Products to comment on results of study SCH-1009 and also, the approximately 50% increase in paliperidone ER Cmax with food a cause for concern regarding the cardiovascular safety of paliperidone. Based on the available data and the cardiorenal input, we may be able to decide whether the proposed labeling for paliperidone ER adequately reflect the cardiovascular risks associated with this drug.

5.2.4 Conclusion Regarding Safety of Paliperidone ER in Schizophrenia

Overall, this submission revealed safety findings of paliperidone consistent with the previously observed safety profile of risperidone. While I acknowledge safety signals raised by the clinical reviewer based on her review of the safety information provided in this submission, the questions imposed to the sponsor to address these issues is deemed unnecessary. We are waiting to receive a consultative report by the Division of Cardiorenal Products on whether there is sufficient QTc and related data, based on the submitted results from the phase 3 placebo-controlled trials and the QT study R076477-SCH-1009, to conclude that paliperidone is reasonably safe. The safety items considered by the Division as needed in prescribing information would be adequately reflected in the labeling.

6.0 WORLD LITERATURE

The sponsor indicated that they discovered 273 publications in their literature search and they noted that their full-text review of 88 of these selected articles revealed no new or remarkable clinical information that affect conclusions about the relevance to the safety of paliperidone. Dr. Brugge reviewed the reference list and some findings were described in her review. She concluded that the safety information of paliperidone are generally not unexpected given they seemed similar to the safety profile of drugs in this class.

7.0 FOREIGN REGULATORY ACTION

To my knowledge, paliperidone is not approved for any indication in any country at this time. We will ask for an update on the regulatory status of paliperidone for the treatment of schizophrenia in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 study sites. DSI recommended that data from these inspected sites appear acceptable. Inspectional findings did not seem to raise any major concern on integrity of study data.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed language has been modified. Our proposed labeling should be included in the action letter.

10.2 Foreign Labeling

At this time, I am not aware that paliperidone is approved for the treatment of schizophrenia anywhere else.

10.3 Action Letter

The approvable letter includes draft labeling and request for phase IV commitment.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that paliperidone ER OROS is effective and appears reasonably safe in the treatment of schizophrenia. I recommend that we issue an approvable action letter. Addendum to this memo will be generated if conclusion changes upon receipt of the consultative report by the Division of Cardiorenal Products. We may consider approval of this NDA contingent on satisfactory responses to the concerns raised by various disciplines, if any, and a mutual agreement between the sponsor and the Agency on language in the labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ni Aye Khin
8/31/2006 03:41:43 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Division of Cardiovascular and Renal Products

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Division of Psychiatry Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
8/8/06		21-999		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Paliperidone		schizophrenia	PDUFA date is 9/30/06

NAME OF FIRM: Johnson & Johnson

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: see attached

SIGNATURE OF REQUESTOR
Steven D. Hardeman, R.Ph.
CPMS
Division of Psychiatry Products
WO Room 4390

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☒ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Reason for Request:

We would appreciate your input and recommendations about QT findings for paliperidone, particularly those reported from study SCH-1009). Specific questions are included in attached document.

Comments/Specific Instructions:

This is a new NDA for paliperidone extended release oral tablets. Please note that this application has been submitted electronically and may be accessed by the EDR. The link is \\Cdsesub1\evsprod\n021999\0000\ Should you have any questions, please contact Steve Hardeman, CPMS, at 301-796-1081. The PDUFA due date for this NDA is September 30, 2006. Dr. Karen Brugge is the medical officer for this NDA. Please see more detailed questions that are attached.

Cardiology Consult Request

NDA: 21-999
Paliperidone ER in treatment of schizophrenia

Paliperidone is a major active metabolite of risperidone which is an atypical antipsychotic agent approved in the treatment of schizophrenia. Both risperidone and paliperidone are centrally active dopamine D2 and 5-HT_{2A} antagonists.

In this NDA for paliperidone, the sponsor has included the results from the following studies:

1) Study R076477-SCH-1009: cardiovascular safety study

This was a double-blind, placebo and active controlled (moxifloxacin 400 mg), randomized study in subjects with schizophrenia or schizoaffective disorder (total N=141). Study subjects were randomized to paliperidone immediate release (IR) or the positive control, moxifloxacin, on Day 1. All subjects received a single dose of placebo on Day 1 in the paliperidone IR treatment group, and on Days 1 to 7 in the moxifloxacin treatment group. In the paliperidone IR treatment group (N=72), subjects received paliperidone 4 mg/day q.d. on Day 2, 6 mg/day q.d. on Day 3, and 8 mg/day q.d. on Days 4 through 8. In the moxifloxacin treatment group, subjects received moxifloxacin 400 mg on Day 8. Both groups were followed off treatment on Days 9 and 10. [Note: Please note the differences in formulations: risperidone is an immediate release formulation while the to-be-marketed formulation of paliperidone is an extended release oral OROS formulation which was also used in the phase 3 clinical studies stated above. The formulation used in study SCH-1009 was the immediate release formulation of paliperidone. It should be noted further that the Cmax ss for paliperidone IR 8 mg qd is 113 ng/mL, approximately 2.5 times the Cmax ss for paliperidone ER 12 mg qd, i.e., 45 ng/mL.]

Table 12 (Day-averaged QTcLD) showed a LS mean difference of 5.5±1.09 ms (90% CI 3.66-7.25) at Day 8 for the paliperidone IR group and a difference of 4.3±0.84ms (90% CI 2.88-5.64) at Day 8 for the moxifloxacin 400 mg group, compared to placebo at Day 1. None of the paliperidone IR subjects showed a QTc increase of greater than 60 ms. None of the paliperidone IR subjects showed prolonged QT values exceeding 450 ms for males and 470 ms for females except that QTcB was prolonged in 7 out of 72 paliperidone IR subjects. [Note: Paliperidone increases the heart rate.]

2) Phase 3 clinical studies (conducted with paliperidone ER):

- Study R076477-SCH-303 (Europe): a 6-week, double-blind, placebo and active controlled (olanzapine 10mg), parallel-group, fixed-dose (6, 9, 12 mg of paliperidone ER) study to evaluate the efficacy and safety of paliperidone ER. Total N=629; N=375 in paliperidone group
- Study R076477-SCH-304 (all U.S. sites): a 6-week, double-blind, placebo and active controlled (olanzapine 10mg), parallel-group, fixed-dose (6, 12 mg of paliperidone ER) study to evaluate the efficacy and safety of paliperidone ER. Total N= 439, N=224 in paliperidone group
- Study R076477-SCH-305: a 6-week, double-blind, placebo and active controlled (olanzapine 10mg), parallel-group, fixed-dose (3, 9, 15 mg of paliperidone ER) study to evaluate the efficacy and safety of paliperidone ER. Total N=614; N=364 in paliperidone group
- Study R076477-SCH-302: a 6-week, double-blind, placebo controlled, flexible dose of paliperidone ER in elderly with schizophrenia. Total N=114; N=76 in paliperidone group

The sponsor indicates that paliperidone ER did not differ from olanzapine or placebo in a pooled analysis of the 3 phase 3 studies in adults.

3) Pivotal BE food effect study:

- Study R076477-P01-1008: The results showed food effects in which approximately 42-46% increase in the Cmax and AUC were observed in the fed compared to the fasted state.

The proposed paliperidone ER dosing regime is 6 mg administered daily in the morning with the recommended daily dose range of 3 to 12 mg.

Questions:

1. Is study SCH-1009 an adequate basis for estimating the QT effects of paliperidone?
2. Are the QT data from study SCH-1009, along with the QT findings from the phase 3 clinical studies with paliperidone, a sufficient basis for concluding that paliperidone ER, at the doses recommended, is adequately safe?
3. Is there any need for additional QT data before reaching a conclusion about the cardiovascular safety of paliperidone ER?
4. Is the roughly 50% increase in paliperidone ER Cmax with food a cause for concern regarding the cardiovascular safety of paliperidone?
5. Does the proposed labeling for paliperidone ER adequately reflect the cardiovascular risks associated with this drug?

Reference:

QT study full report: Mod5.3.5.4\R076477-SCH-1009

- Module 5.3.5.4\R076477-SCH-1009\Section7.2.1.1
- Table 12: Day-Averaged QTcLD: Least Square Mean Differences From Day 1
- Table 15: Number of subjects with a maximum change in QTc interval of 30 to 60 ms or >60 ms. (Attachment 3.4)
- Table 16: Number of subjects with a maximum QTc interval that was borderline or prolonged (Attachment 3.5)
- Attachment 3.6: Number (%) of Subjects With a Maximum QTc Interval of 450 ms or Greater by Study Day and Time Postdose.

Tabular Listing of all studies and linkage:
\\Cdsesub1\evsprod\n021999\0000\m5\52-tab-list

Phase 3 clinical study reports:
\\Cdsesub1\evsprod\n021999\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5351-stud-rep-contr

Pivotal BE food effect study report: Mod5.3.1.2\R076477-P01-1008

Proposed labeling (word version): \\Cdsesub1\evsprod\n021999\0000\m1\us

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/s/

Steve Hardeman
8/10/2006 01:16:34 PM

CLINICAL REVIEW

Application Type:	NDA 21-999
Submission Number Code and Materials Reviewed:	N005 (sections not previously reviewed in the original NDA review), N007, N006 (sections as specifed in the review), Responses to other Questions, as specified in the review
Letter Dates:	6/15, 06, 6/27/06, 6/15/06, respectively and see review f or additional dates
Reviewer Name	Karen Brugge, MD
Review Completion Date	8/18/06
Established Name	Paliperidone
(Proposed) Trade Name	[redacted]
Therapeutic Class	Atypical Antipsychotic
Applicant	Johnson & Johnson
Priority Designation	Standard
Formulation	Extended Release OROS® oral tablets
Proposed Dosing Regimen	6 mg administered daily in the morning, may benefit from lower or higher doses within the recommended daily dose range of 3 mg to 12 mg once, daily.
Indication	Schizophrenia
Intended Population	Adults with Schizophrenia

I. Introduction and Background

The following subsections summarize the sponsor's responses to inquiries (that were not included in the original NDA review). The final section of this review summarizes a section found in the 210-safety update report submission under this NDA in which the sponsor added new information to 15 narratives (the section reviewed in the 210 safety update report, as specified later in this introductory and background section).

Reviewer comments are italicized and are followed by reviewer recommendations (italicized) in the case that the Agency grants an approvable action on this NDA.

Questions and comments are conveyed to the sponsor that can be found in an 8/2/06 documents submitted in DFS under this NDA. The following summarizes the sources of information continue responses to questions conveyed to the sponsor that are summarized in this review, unless otherwise specified:

- Sections of N005 (some sections of this submission were previously reviewed in summarized in the original review of this NDA).
- Results from an EKG study, Study SCH-1009, found in N007 (dated 6/27/06).
- E-mailed responses dated 7/15/06, 7/21/06, and 7/26/06 in response to Questions 2, 3, and Questions 4 and 5, respectively (these questions were conveyed to the sponsor in an e-mail communication dated 6/28/06 which is included in the 8/2/06 correspondence document submitted under the NDA in DFS).
- New information was added to narratives of 15 subjects that were found in appendix 3.6 of the Summary of Clinical Safety Section (SCS) starting on page 1709 of the SCS in the 210 SUR N006 submission.

Before summarizing the sponsor's response to inquiries, the next section provides information about a subject with serious adverse events (SAEs) leading to an early withdrawal (adverse dropout also referred to as ADO), in which the subject's past history was described in the original review as including a history of one of the SAEs (psychogenic polydipsia), yet the subject's narrative indicates that this subject did not have a history of this condition.

II. Subject 500108

This section of this review describes a subject with hyponatremia (sodium level of 117 mmol, serum osmolality of 240; 275-295 within normal limits of which units were not found) that resolved within 2 days with treatment) and psychogenic polydipsia, convulsion and pneumonia aspiration reported as SAEs and that lead to early cessation of Pal treatment in a subject with no past history of any related events. This subject was previously described in the review of the NDA but had indicated that this subject had a past history of psychogenic polydipsia. The narrative indicates specifically that this subject did not have a prior history of this condition.

Reviewer Comment
The overall conclusion of this subject does not change from that previously described in the review of the original NDA submission. Psychogenic polydipsia was likely to be the diagnosis. However, in the absence of additional clinical information (e.g. results of a diagnostic work-up

to rule out other causes, such as urine osmolality) the etiology of the hyponatremia is not certain. Psychogenic polydipsia is reported to occur in this patient population and can lead to the type of complications that this patient developed. This event also appears to be an isolated case.

III. N007 Amendment Submission Response to a Request Regarding Subjects with Potential Vital Sign Related Events

N007 provides a response to a request for information on any subject with symptomatic bradycardia, tachycardia, hypotension, orthostatic hypotension and syncope. The sponsor was given examples of subjects and comments about our concerns in identifying subjects, as follows (copied from an 8/2/06 DFSed Telecon/e-mailed correspondence document under NDA 21999 N000):

> "Syncope and potential pro-arrhythmic effects: Patient 300541 in study 304 is described as having sinus pauses of up to 8 seconds but a description of this subject could not be found in the pro-arrhythmic section of the SCS or in any other in-text section of the SCS.
>
> Subject 201805 in Study -303 (a 33 year old male) had 12 mg daily Pal treatment discontinued on Day 7 who had an SAE of tachycardia that was first noted on Day 4 and reached a HR of 120 bpm supine (124 bpm standing) compared to 71 bpm (per ECG) at baseline (84 bpm supine at baseline). The subject also developed "hypotension" in which Day 4 BP was 100/65 mmHg, supine (115/75 standing) compared to 135/65 mmHg, supine at baseline and decreased further to 85/55 mmHg, supine, on Day 6 (80/50 standing). Supine BP of 115/80 mmHg and HR of 93 bpm on day 7. The tachycardia prolonged his hospitalization. Tachycardia was reported to resolve by 12 days and hypotension by 3 days without treatment. ALT was also reported to be "increased" during the study.
>
> Subject 201803 in Study -303 (33 year old male) had a SAE of tachycardia with increased heart rate first noted on Day 7 of 6 mg daily of Pal treatment compared to baseline values while BP generally did not change from baseline vales. This subject was not described as having orthostatic hypotension (on page 146 of the CSR). His baseline supine and standing heart rates were 72 and 76 bpm, respectively compared to supine and standing heart rates of 106 and 130, respectively on Day 8 of treatment. Metoprolol treatment was started on Day 10 and given for 11 days. Tachycardia resolved by 14 days. Paliperidone treatment was over 21 days, then the subject withdrew from the study on Day 22 "due to consent withdrawn" with an ECG heart rate of 73 bpm on that day.
>
> We are interested in a listing of patients that were asymptomatic at baseline but who went on to have syncope, symptomatic bradycardia or tachycardia or symptomatic hypotension. Would it be possible for you to make a listing of these patients (with whether they were SAE, DAE or both along with their verbatim and thesaurus term) and a page number reference to the narrative?"

Response and Reviewer Comments: *The sponsor's response (in N008) was confusing regarding the methodology they employed for generating summary tables that show the incidence of subjects they identified. The in-text summary tables did not provide subject numbers but only the incidence of subjects in only the Phase III datasets (we asked for results of all safety datasets).*

Attached to their response were approximately 1000 pages of appendices of line listings that were difficult to understand in conjunction with their explanation of methods they employed for generating these listings. The only narrative information provided was of selected serious adverse events (SAEs) and adverse dropouts (ADO) that were captured by their special search of cases. These narratives were included among the narratives of SAEs and ADOs provided in the original NDA submission. The sponsor's summary of their search results are difficult to interpret, as in the following example.

The following is an example of an in-text summary table that is followed by their comments and conclusions regarding this table.

Table 1: Number of Subjects With a Symptomatic Vital Sign/Heart Rate Abnormality of Inte
Pooled Double-Blind Studies
(Studies R076477-SCH-303, SCH-304, and SCH-305: Safety Analysis Set)

Abnormality	Placebo (N=355)	Total Paliperidone (N=963)	Olanzapine (N=364)	To (N=1
Total number of subjects with any abnormality	7	32	10	4
Symptomatic bradycardia	3	7	6	1
Symptomatic hypotension	1	7	0	8
Symptomatic orthostatic hypotension	0	4	0	4
Symptomatic tachycardia	2	16	2	2
Syncope	1	7	2	1

Note: Some subjects had an abnormality in more than one category
Cross Reference: Attachment 2.5.

Per the predefined criteria, a total of 49 distinct subjects out of 1,682 (3%) subjects in the pooled double-blind studies were identified as symptomatic during treatment but asymptomatic at baseline/screening (ER OROS paliperidone 3%, 32/963; placebo 2%, 7/355; olanzapine 3%, 10/364). The data for these 49 subjects identified with a symptomatic abnormality underwent additional clinical review to assess causality. For 12 of these 49 subjects identified as symptomatic, there may have been a cause for the abnormality other than study drug (e.g., concomitant medication or medical condition), including 7 of 32 subjects treated with ER OROS paliperidone, as well as 3 of 7 placebo subjects and 2 of 10 olanzapine subjects. For the remaining subjects, there was insufficient information to draw conclusions.

The basis for the sponsor's conclusions is not clear, since the rationale for conclusions cannot be found in their response (as in the above example, corresponding subject numbers and relevant narrative information that correspond to conclusions such as the conclusion that there may have been a non-drug-related cause of the symptoms of 12 out of 49 subjects could not be found in the submission). The type of relevant information that would have been helpful but that could not be found on the subjects include information such a clinical data, the differential diagnosis and work-up of a given subject, potential risk factors and other information relevant to the potential etiologies). It is also not clear why information was insufficient on the other subjects and why this information was not obtained or provided. Only the narratives of selected ADOs or SAEs were provided and information was limited in some of these narratives sometimes (e.g. a

description of "syncope," the discharge summary and other key relevant information in subject 300541). The following table lists the subjects that had narratives which were the subjects that were reported as ADOs or having SAEs (copied from the N008 submission).

Table 2: Subjects Identified With a Symptomatic Vital Sign/Heart Rate Abnormality for Whom a Narrative Was Previously Submitted: Studies R076477-SCH-303, SCH-304, and SCH-305

Study	Subject Number	Treatment Group	Event Identified Per Methodology[a]	Reason for the Narrative Submitted in NDA 21-999\0000\ Mod 2.7.4	Completion/ Withdrawal Information
SCH-304	300541	ER OROS PAL 12 mg/day	Syncope, Symptomatic bradycardia	D/C due to exacerbation of psychosis (Day 5). SAEs dizziness and hypotension (Day 5), and bradycardia and delay in pulse (coded to heart rate irregular) (Day 6)	Withdrawn on Day 6
SCH-305	500102	ER OROS PAL 9 mg/day	Symptomatic hypotension	D/C due to dizziness, impaired memory, nausea, headache, (Day 1) and SAE tachycardia (Day 3)	Withdrawn on Day 12
SCH-305	500518	Placebo	Symptomatic bradycardia	D/C due to hyponatremia (Day 14) and SAE rule out primary polydipsia (coded to polydipsia) (Day 15)	Withdrawn on Day 16
SCH-303	200966	Olanzapine 10 mg/day	Syncope	D/C due to elevated serum ALT values and elevated serum AST values	Withdrawn on Day 17
SCH-304	300137	Olanzapine 10 mg/day	Syncope	D/C due to SAEs QT prolonged and electrolyte disturbance	Withdrawn on Day 11
SCH-305	501519	Olanzapine 10 mg/day	Symptomatic bradycardia	D/C due to sedation	Withdrawn on Day 36

ALT = alanine aminotransferase, AST = aspartate aminotransferase, D/C = discontinued, SAE = serious adverse event

[a] Please see Attachment 1 for the detailed description of methodology.

The appendices of the sponsor's response were over 1300 pages long. The undersigned reviewer conducted a word search in the PDF submission for "syncope." Over approximately 40 pages within the appendices were found to have this term.

Reviewer Recommendation

It is recommended that the sponsor be asked to provide a line listing of subjects in each treatment group in each study of each safety dataset (Phase I-III) with syncope (reported as a verbatim or preferred term) in all safety datasets that includes the following information:

- *Subject number*
- *Verbatim and preferred terms*
- *Whether or not the subject was an ADO or SAE with corresponding verbatim and preferred terms*
- *A hyperlink and specification of exact location of a narrative description of the subject.*

It is recommended that the sponsor provide a narrative description of each of the above subjects that includes any clinically relevant information (e.g. diagnostic test results, clinical data, risk factors, and other information) regarding potential etiologies of the

syncopal event and that provides a clinical interpretation of the event (e.g. including differential diagnosis) with data to support to conclusions (e.g. results of a diagnostic work-up, vital sign data, risk factors). The narrative information should also include a discharge summary of any subject to was hospitalized due to any type of adverse event (i.e. adverse events or clinical findings that led to hospitalization, prolonged hospitalization, or transferred to a specialized unit, or an emergency room evaluation).

A request for the above information (line-listings and narratives) is recommended for each of the following types of events:

- *Any subject with heart rate below 50 bpm (or had a related AE reported, such as bradycardia) during treatment (with normal values at baseline).*
- *Any subject with a systolic blood pressure below 100 (or had a related AE, such as low blood pressure) during treatment (with normal values at baseline) that did not have orthostatic hypotension.*
- *Any subject with a systolic blood pressure below 100 (or had a related AE, such as low blood pressure) during treatment (with normal values at baseline) that also had orthostatic hypotension.*
- *Any subject with sinus pause, PR prolongation or AV block or a related arrhythmia (even reported as an AE or as reported by EKG assessment) during treatment (that was not present at baseline).*
- *Any subject with tachycardia (with a heart rate over 120 bpm are reported as a related AE, such as tachycardia, sinus tachycardia, as examples) in the absence of concurrent orthostatic hypotension (that was not present at baseline).*

IV. Sections of N005 Responding to Inquiries of Elevations of CPK Levels

The following paragraphs provide background information regarding the potential drug effect on CPK levels in which comments are provided from the perspective of the undersigned reviewer and therefore is provided in a televised text.

The sponsor was asked about a potential CPK signal observed in high versus low OROS treated Phase I subjects that showed a greater mean elevation after a high dose of OROS Pal compared to levels obtained after receiving a low-dose of OROS Pal (refer to the original NDA review for details under section 7.1.7.3.1). Schizophrenia Phase III trials (double-blind, short-term trials and open-label longterm trials) showed highly variable CPK levels across treatment groups, across subjects and fluctuate came levels over time such that results were difficult to interpret. While these observations could be reflecting elevations related to the patient population rather than being drug-related, highly variable and fluctuating CPK levels can lead to difficulties in detecting a potential drug effect (as discussed previously in the original NDA review).

The sponsor was asked about the above potential signal in healthy subjects in Phase I trials (found in the safety dataset of 17-Phase I pooled studies, as described in the review of the original NDA submission). The sponsor was also asked to provide descriptive statistical results

and incidence of outliers for other treatment conditions (e.g. placebo, risperidone), since this information could not be found in the original NDA submission (as described in the original NDA review).

Response: The sponsor's response indicates that only some of the Phase I trials collected post-dose CPK data and that Phase I trials with placebo or risperidone treatment conditions were not among these trials (i.e. CPK data was not collected in trials with a placebo or risperidone treatment condition).

The Phase I trials that included post-treatment CPK assessments, had blood samples collected at the following time-points (these trials were cross-over trials generally involving several single-dose treatment periods and between-treatment-period washout intervals of at least several days):

- Screening
- End-of-study visit (at 5 days post-dose for Studies –P01-1008 and P01-1007 and at 4-8 days post-dose for other studies).
- Prior to dosing on selected treatment days in a few of the trials (trials generally employed a multiple day washout period)
- One study also had a 48 hour post-dose laboratory assessment for Period 1 only (Study –P01-1006).

A total of 177 subjects in the pooled Phase I dataset had CPK levels at a time-point after dosing.

The following summarizes the grouping of subjects by treatment condition for the Phase I safety dataset that included subjects receiving high and low dose OROS pal and/or IR pal as follows (copied from the submission):

Treatment Group	Description
Placebo	All placebo treatments
Paliperidone IR:	All immediate-release (IR) treatments, including intravenous (i.v.) injection, ^{14}C labeled oral solution, oral solutions and tablets with racemic mixtures, oral solutions of (+) and (-) enantiomers
Paliperidone Other:	All experimental formulations containing paliperidone doses of 2 to 6 mg (includes osmotic modules, paliperidone flat and ascending profiles, coated OROS, [redacted]OROS, and al[redacted] formulations)
Paliperidone OROS, Low Dose:	All 3 to 6 mg paliperidone doses using Phase 1 (or SLOW OROS – 2 mg tablets) Phase 3, and commercial to-be-marketed ER OROS paliperidone formulations
Paliperidone OROS, High Dose:	All 9 to 15 mg paliperidone doses using Phase 1 (or SLOW OROS – 2 mg tablets), Phase 3, and commercial to-be-marketed ER OROS paliperidone formulations; a first day of placebo in a 1-week paliperidone group in Study R076477-SCH-101 followed by 12 mg paliperidone OROS
Risperidone:	All 2 to 8 mg oral risperidone treatments, including risperidone ascending profiles, osmotic modules, oral solutions, and IR tablets

The incidence of outliers on high CPK levels in the combined safety dataset was as follows:

- 1% of low dose OROS pal subjects (1/76 subjects)
- 3 % of high dose OROS pal subjects (4/123 subjects)
- 0 IR Pal treated subjects met outlier criteria, while noting that the dose given to these subjects was generally lower than the low and high dose OROS treatment conditions, as shown in the previous table (1-3 mg of which a few subjects received drug intravenously). Furthermore, only 21 subjects received the IR Pal treatment.

The sponsor provided narrative descriptions for the above 5 subjects who were outliers on high CPK levels (Attachment 1 of this review provides a copy of these narratives). CPK level values were also provided for each assessment time-point for each of these subjects, which will be shown later.

The sponsor concludes that there were related events that "could explain the abnormality" in each of the 5 subjects, such that elevations in CPK levels did not appear to be drug-related in these cases.

Since the above 5 subjects came from either Study –P01-1008 or Study –P01-1010 the following additional information about these 2 trials is provided below:

- The majority of High and Low dose ER Pal subjects in the Phase I safety dataset came from either or both of these 2 trials as follows (copied from a section of the sponsor's table):

Treatment group	Study
PALI OROS low dose (n=76)	P01-1006 (n=20) P01-1007 (n=4) P01-1010 (n=49) SIV-101 (n=3)
PALI OROS high dose (n=127)	P01-1008 (n=80) P01-1010 (n=47)

- The study design of each of these 2 trials is shown in the table below (copied from a summary table that was provided by the sponsor).

Study	Study design/enrolment status
R076477-P01-1008 Final bioequivalence and food effect (ER)	SD, OL, randomized, 3-way CO in healthy males / single oral doses of 15 mg (9+3+3 mg) PAL ER, 15 mg PAL ER tablet (fed or fasting) / BE of Phase 3 formulation (9+3+3 mg) vs. highest strength (15 mg) of commercial formulation, food effect on highest strength commercial formulation. No. Subj. enrolled: 80 Treated with Paliperidone: 80
R076477-P01-1010 Dose proportionality (ER)	SD, OL, randomized, 5-way CO in healthy males / oral dose, 3, 6, 9, 12 or 15 mg PAL ER tablet (fasting) / dose proportionality. No. Subj. enrolled: 50 Treated with Paliperidone: 50

Reviewer Comment. *The sponsor used a cut-off criterion of >990 U/l. The rationale for selecting this cutoff criterion for a healthy Phase I subject population cannot be found in their response. Such a remarkably abnormal value may not be the optimal cut-off criterion for a generally healthy population for detecting a potential drug-related effect.*

It is also not clear if greater group mean CPK values in the high OROS compared to the low OROS and the IR Pal groups would still be revealed if data from the above outlier subjects were excluded from the analyses. In any case, the incidence of outliers was higher in the High dose compared to the low dose OROS Pal conditions and suggests a dose-dependent effect of Pal on CPK levels (as previously described in the review of the original NDA).

Higher group mean CPK values were also observed in the high OROS group compared to the IR Pal, as previously described. This observation may be also reflecting the dose-dependent drug effect, since the IR Pal condition involved lower single dose levels (1-3 mg) than were given to a number of subjects in the low OROS condition (3-6 mg). It is also important to note that the IR pal condition used shorter acting formulations, including an intravenous route of administration in some subjects, in contrast to the longer acting, oral OROS treatment condition. Therefore, these other confounding variables may have also influenced treatment group differences on CPK

values. Another consideration is in the small sample size of the IR pal condition which consisted of only 21 subjects. Finally, it is not clear if the above positive findings are reproduceable.

While several subjects may have had events that might account for the CPK levels at least a role of Pal is possible for at least the following reasons (see Attachment 1 of this review for a copy of the individual-subject narrative descriptions):

- *Subject 101017 had "chest pain (muscular)" thought to account for the elevations in CPK, yet it is not clear from the narrative whether or not this muscular-related event was drug-related (e.g. muscular pain may have occurred due to a dystonic like or other extrapyramidal related event which in turn, could be associated with elevations in CPK). Several adverse dropouts due to extrapyramidal side effects reported in Phase I subjects could have been associated with elevations in CPK.*
- *While a few subjects also had abnormally high CPK levels at baseline, these baseline values did not meet outlier criteria, yet remarkable CPK values (values that met outliers criteria including values of up to 8240 U/l) were revealed after these subjects received multiple single-dose treatment periods and they generally received the higher dose level treatment conditions (e.g. 12 and 15 mg dose-levels). One exception is subject 101038 in which this subject met outlier criteria after a single treatment period. Yet, the highest dose level (15 mg) was given on this first treatment period, while lower doses were given on subsequent treatment periods. Laboratory CPK results for each time-point in each subject is shown later in this review.*
- *Attachment 1 of this review provides the narrative descriptions of the 5 subjects.*
- *Although the washout interval between treatment periods was for several days (as previously described), it is not clear how soon after treatment the CPK values increased, since CPK levels were not obtained until the next treatment prior to dosing for that given treatment period. One might also expect a possible lag in the rise of CPK levels following dosing, as can be observed with some drugs that induce elevations and liver function tests, based on the experience of the undersigned reviewer.*
- *Given the above comment of a potential lag period that the undersigned reviewer has observed with some drugs inducing elevations in liver function tests, it is also notable that 4 out of the 5 subjects also showed elevations in liver functions tests (the above subject with muscular chest pain did not have elevated liver functions test values). Yet, several of these subjects also had other AEs that suggested the possibility of a systemic illness (e.g. one subject had "common cold" AE reported).*
- *A clear reason for elevated CPK and elevations in LFTs in the 4 out of 5 subjects showing these abnormalities could not be found in the narrative descriptions (e.g. a diagnostic work-up with results such as a alcohol abuse, viral hepatitis based on CBC and hepatitis antigen, antibody work-up, among others).*

Individual subject CPK levels over time for each of the 5 above subjects who met the outliers criteria for elevated CPK are shown below (as copied from the submission; see Attachment 1 for narratives and for treatment conditions for each of the following corresponding treatment periods):

Output [redacted] 1001A8: Subjects With Treatment-Emergent Markedly Abnormal Laboratory Values - Phase 1/2a Studies (continued)

Analysis Set: Safety
Analysis Group: Healthy Volunteers-SD
Lab Type: Chemistry
Param: Creatine kinase, U/L
Marked Abnormal Range (Unit): N/A - 990 (U/L)

Markedly Abnormal Sex Flag	Study Id	Subject Number	Actual Date of Sample	Actual Time of Sample	Scs Treatment Group	Scs Visit	Lab Visit Type	Reported Value	Change	
Male	R076477-P01-1008	100843	09Sep2004	11:40	NONE	Screening	Scheduled	76		N
			15Sep2004	8:07	NONE	Baseline	Scheduled	62		N
			28Sep2004	8:02	PALI OROS HIGH DOSE	Post dose	Scheduled	69	7	N
			05Oct2004	7:30	PALI OROS HIGH DOSE	Post dose	Scheduled	8246	8184	H
			12Oct2004	9:01	PALI OROS HIGH DOSE	Post dose	Scheduled	239	177	N
	R076477-P01-1010	101012	30Jul2004	11:14	NONE	Screening	Scheduled	434		N
			09Aug2004	9:21	NONE	Baseline	Scheduled	822		N
			19Aug2004	9:22	PALI OROS HIGH DOSE	Post dose	Scheduled	489	-333	N
			30Aug2004	9:11	PALI OROS HIGH DOSE	Post dose	Scheduled	577	-245	N
			31Aug2004	16:23	PALI OROS HIGH DOSE	Post dose	Unscheduled	263	-559	N
			09Sep2004	9:13	PALI OROS HIGH DOSE	Post dose	Scheduled	596	-226	N
			20Sep2004	9:15	PALI OROS LOW DOSE	Post dose	Scheduled	3045	2223	H
			24Sep2004	9:19	PALI OROS LOW DOSE	Post dose	Scheduled	433	-389	N
		101015	04Aug2004	15:03	NONE	Screening	Scheduled	222		N
			10Aug2004	8:30	NONE	Baseline	Scheduled	82		N
			20Aug2004	8:30	PALI OROS LOW DOSE	Post dose	Scheduled	76	-6	N
			31Aug2004	8:30	PALI OROS LOW DOSE	Post dose	Scheduled	77	-5	N
			10Sep2004	8:30	PALI OROS HIGH DOSE	Post dose	Scheduled	89	7	N
			21Sep2004	8:30	PALI OROS HIGH DOSE	Post dose	Scheduled	2885	2803	H
			23Sep2004	8:41	PALI OROS HIGH DOSE	Post dose	Unscheduled	1756	1674	H
			25Sep2004	8:36	PALI OROS HIGH DOSE	Post dose	Scheduled	1178	1096	H
		101017	30Jul2004	15:40	NONE	Screening	Scheduled	240		N
			10Aug2004	8:40	NONE	Baseline	Scheduled	133		N
			20Aug2004	8:40	PALI OROS HIGH DOSE	Post dose	Scheduled	94	-39	N
			31Aug2004	8:40	PALI OROS HIGH DOSE	Post dose	Scheduled	143	10	N
			10Sep2004	8:40	PALI OROS HIGH DOSE	Post dose	Scheduled	3394	3261	H
			21Sep2004	8:40	PALI OROS LOW DOSE	Post dose	Scheduled	135	2	N
Male	R076477-P01-1010	101017	25Sep2004	9:05	PALI OROS LOW DOSE	Post dose	Scheduled	132	-1	N
		101038	11Aug2004	10:15	NONE	Screening	Scheduled	140		N
			13Aug2004	9:29	NONE	Baseline	Scheduled	128		N
			23Aug2004	9:25	PALI OROS HIGH DOSE	Post dose	Scheduled	3173	3045	H
			03Sep2004	9:25	PALI OROS HIGH DOSE	Post dose	Scheduled	470	342	N
			13Sep2004	9:25	PALI OROS LOW DOSE	Post dose	Scheduled	151	23	N
			24Sep2004	9:20	PALI OROS HIGH DOSE	Post dose	Scheduled	117	-11	N
			28Sep2004	11:44	PALI OROS LOW DOSE	Post dose	Scheduled	178	50	N

It is also important to note that it is not clear why elevations were sometimes observed after longterm term treatment in subjects in the open-label trials (e.g. consider lack-of-efficacy in which subjects become acutely psychotic and agitated for example, or drug-related adverse events or other potential events that may account for this observation).

In conclusion, the sponsor's response does not provide adequate assurance that a potential OROS Pal-related signal for elevations in CPK does not exist. Refer to the original NDA review for further comment on this potential signal relevant to the Phase III patient population. Also the original NDA review describes subjects with elevations in CPK and LFTs (liver function tests) that may or may not be inter-related.

Reviewer Recommendation. *As previously advised in the original NDA review, it is recommended that this issue be resolved before considering a final approval action on this NDA (in the case the Agency grants an approvable action). If the sponsor cannot provide convincing data to explain non-drug-related reasons for elevations in CPK in their trials, it is also recommended that labeling inclu* [redacted]

[redacted] *As recommended in the review of the original NDA submission this subsection under Warning and Precautions should be included for describing elevations observed in liver function tests in some subjects of the Phase I-III trials. This section should also indicate that sometimes these elevations were also associated with elevations in CPK.*

V. Selected Responses to Inquiries about ECG Study –SCH-1009

Results and Reviewer Comments.
Refer to the review of the original NDA for details on the ECG Study SCH-1009. The sponsor was asked several questions about results from this study. The most revealing results were provided in their response that included the following information (some of this information was provided in recent e-mails from the sponsor of which a submission under the NDA is pending at the time of this writing):

- *Raw mean and least square mean QT and QTc interval values of each gender in each treatment group were requested for data-points that correspond to data points shown in the sponsor's Tables 108 and 109 found in the CSR of this study that summarize their results (also shown in the clinical review of the original NDA under Section 7.1.12 A).*
- *The sponsor was also asked to provide least square mean values for QTc interval (of each treatment group as shown in Tables 108 and 109) based on their statistical analyses of results (only results of QTcLD could be found in the original NDA, but not for QTcF, QTlc or others as described in the review of the original NDA for details).*

The most remarkable QTc prolongation effects were generally observed at approximately 1 ½ hour post-dose on Day 2 (first day of Pal treatment which was given as 4 mg IR), Day 4 (first day of the 8 mg dose-level), Day 8 (after 4 days of 8 mg/day) in the Pal group. The maximal group mean increases (from the averaged pre-dose values) that were generally observed at these time-points were approximately 10-12 msec for raw group mean QTcLD, QTlc, and QTcF in male and female subgroups with some exceptions as shown in tables below (results of QTcB were not requested since this was considered least informative, for reasons discussed in the review of the original NDA). These results of raw group mean values were generally similar to results of least square group mean values of QTc (QTcF and QTcLD) but maximal group mean increases (also observed at the 1/12 hour post-dose time-point on Days 2, 4 and 8) were generally lower than the corresponding raw group mean QTc values (least square mean values were generally approximately one millisecond less than the raw group mean values).

Gender differences can also be seen when examining the results shown in the tables below. Males appear to show greater maximal mean changes when examining tables showing results by multiple post-dose time-points that include time-points near Tmax. However, females appear to show a greater duration of QTc prolongation when examining the averaged QTc mean increases on a given treatment day or when examining the data by multiple post-dose time-points (refer to the tables below).

The Sponsor's Summary Tables Provided in Their Response

The following is a copy of sections of the sponsor's summary tables for the raw QTc mean changes at various post-dose time-points during treatment in the Pal group (the results of the moxifloxacin group are not shown) for each gender (as provided in a 6/29/06 e-mail from the sponsor, the sponsor was asked to submit results as an amendment under the NDA, of which remains pending at the time of this writing). These results correspond to the results of Table 109 in the CSR and shown in Section 7.1.12 of the review of the original NDA (this table as found in the original NDA only showed results of least square mean changes in QTcLD which were not provided for each gender subgroup within each treatment group and were not provided for other methods for calculating QTc).

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcLD (ms)
Treatment Arm: IR Paliperidone
Sex: Male

	Day 2 (PALI 4 mg)		Day 3 (PALI 6 mg)		Day 4 (PALI 8 mg)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	0.3 (1.41)	(-2.10; 2.69)	-0.5 (1.30)	(-2.68; 1.74)	0.2 (1.35)	(-2.07; 2.49)
30min	4.1 (2.05)	(0.64; 7.58)	3.1 (1.70)	(0.21; 5.96)	5.9 (1.65)	(3.15; 8.74)
1h	4.9 (1.70)	(1.99; 7.73)	5.5 (1.59)	(2.79; 8.16)	6.4 (1.58)	(3.75; 9.08)
1h30min	10.4 (2.03)	(7.02; 13.87)	8.2 (1.83)	(5.11; 11.28)	11.5 (2.22)	(7.78; 15.27)
2h	6.0 (1.71)	(3.08; 8.86)	5.8 (2.07)	(2.31; 9.30)	7.5 (1.81)	(4.44; 10.56)
2h30min	3.8 (1.49)	(1.23; 6.27)	4.5 (1.37)	(2.16; 6.79)	5.5 (1.63)	(2.77; 8.29)
3h	4.1 (1.86)	(0.99; 7.29)	4.2 (1.77)	(1.23; 7.21)	8.1 (2.33)	(4.12; 11.99)
3h30min	3.9 (1.59)	(1.21; 6.57)	0.9 (1.79)	(-2.17; 3.89)	5.2 (1.61)	(2.48; 7.91)
4h	3.1 (1.85)	(-0.02; 6.24)	3.1 (1.70)	(0.23; 5.99)	4.3 (1.55)	(1.71; 6.95)
6h	1.8 (1.72)	(-1.11; 4.72)	-0.8 (1.86)	(-3.89; 2.39)	1.5 (1.49)	(-1.04; 3.99)
12h	2.1 (1.31)	(-0.16; 4.28)	-0.9 (1.70)	(-3.81; 1.93)	1.3 (1.69)	(-1.61; 4.12)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcLD (ms)
Treatment Arm: IR Paliperidone
Sex: Male

	Day 8 (PALI 8 mg)		Day 9 (Posttreatment)		Day 10 (Posttreatment)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	1.7 (1.54)	(-0.93; 4.28)	1.2 (2.06)	(-2.33; 4.64)	0.1 (1.52)	(-2.51; 2.63)
30min	6.8 (1.76)	(3.78; 9.72)	5.6 (1.78)	(2.63; 8.64)	7.0 (1.58)	(4.33; 9.67)
1h	7.8 (1.51)	(5.26; 10.35)	5.1 (1.73)	(2.17; 8.00)	2.3 (1.75)	(-0.67; 5.23)
1h30min	11.7 (1.81)	(8.66; 14.79)	5.4 (2.28)	(1.59; 9.30)	3.1 (2.28)	(-0.80; 6.91)
2h	9.1 (1.63)	(6.38; 11.90)	5.6 (1.88)	(2.44; 8.78)	1.4 (1.88)	(-1.81; 4.53)
2h30min	7.5 (1.91)	(4.32; 10.77)	1.5 (1.87)	(-1.65; 4.68)	0.1 (1.60)	(-2.57; 2.85)
3h	7.8 (1.97)	(4.51; 11.16)	3.2 (1.70)	(0.33; 6.06)	0.9 (1.76)	(-2.12; 3.84)
3h30min	4.6 (2.31)	(0.71; 8.51)	3.8 (1.84)	(0.65; 6.85)	1.0 (1.56)	(-1.64; 3.64)
4h	5.8 (1.44)	(3.38; 8.23)	1.9 (1.39)	(-0.48; 4.21)	2.2 (1.66)	(-0.64; 4.97)
6h	4.0 (1.59)	(1.35; 6.71)	1.8 (1.64)	(-1.02; 4.52)	0.3 (1.53)	(-2.33; 2.83)
12h	3.7 (1.40)	(1.34; 6.08)	3.6 (1.60)	(0.88; 6.30)	3.2 (1.56)	(0.54; 5.81)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcLD (ms)
Treatment Arm: IR Paliperidone
Sex: Female

	Day 2 (PALI 4 mg)		Day 3 (PALI 6 mg)		Day 4 (PALI 8 mg)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	4.9 (3.04)	(-0.88; 10.63)	2.6 (3.55)	(-4.10; 9.35)	2.4 (3.50)	(-4.26; 9.01)
30min	7.2 (2.50)	(2.14; 12.20)	2.0 (3.01)	(-3.84; 7.84)	3.3 (4.39)	(-5.24; 11.82)
1h	5.1 (3.90)	(-2.27; 12.52)	-1.1 (5.36)	(-11.28; 9.03)	1.9 (3.81)	(-5.33; 9.08)
1h30min	2.1 (3.22)	(-4.11; 8.40)	0.1 (4.43)	(-8.26; 8.51)	1.0 (4.68)	(-7.87; 9.87)
2h	2.1 (2.55)	(-2.81; 7.10)	-0.6 (3.51)	(-7.28; 6.03)	6.1 (4.82)	(-3.00; 15.25)
2h30min	1.6 (3.71)	(-5.40; 8.65)	2.1 (4.65)	(-6.69; 10.94)	-0.1 (5.18)	(-10.21; 9.92)
3h	3.5 (2.80)	(-1.81; 8.81)	-3.6 (3.63)	(-10.50; 3.25)	2.9 (5.30)	(-7.45; 13.16)
3h30min	1.4 (2.96)	(-4.24; 6.99)	-4.6 (2.32)	(-9.02; -0.23)	-5.3 (4.04)	(-13.14; 2.56)
4h	2.0 (3.37)	(-4.38; 8.38)	-2.8 (3.05)	(-8.53; 3.03)	-2.7 (4.71)	(-11.87; 6.44)
6h	2.6 (5.40)	(-7.60; 12.85)	-3.5 (4.94)	(-12.86; 5.86)	0.6 (5.35)	(-9.51; 10.76)
12h	1.0 (1.76)	(-2.34; 4.34)	-0.4 (2.33)	(-4.79; 4.04)	1.8 (2.48)	(-2.94; 6.44)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcLD (ms)
Treatment Arm: IR Paliperidone
Sex: Female

	Day 8 (PALI 8 mg)		Day 9 (Posttreatment)		Day 10 (Posttreatment)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	6.4 (3.95)	(-1.11; 13.86)	5.8 (4.34)	(-2.48; 13.98)	3.8 (2.86)	(-1.68; 9.18)
30min	8.0 (3.49)	(1.22; 14.78)	1.1 (4.57)	(-7.75; 10.03)	8.0 (5.45)	(-2.59; 18.59)
1h	9.4 (4.63)	(0.61; 18.14)	-0.1 (4.04)	(-7.78; 7.53)	1.8 (3.86)	(-5.57; 9.07)
1h30min	7.4 (4.69)	(-1.52; 16.27)	2.8 (4.34)	(-5.47; 10.97)	1.3 (3.79)	(-5.93; 8.43)
2h	7.9 (3.58)	(1.10; 14.65)	3.1 (3.88)	(-4.40; 10.69)	3.0 (1.69)	(-0.20; 6.20)
2h30min	8.4 (4.48)	(-0.10; 16.85)	2.0 (3.74)	(-5.09; 9.09)	1.8 (3.33)	(-4.55; 8.05)
3h	7.0 (5.58)	(-3.57; 17.57)	4.3 (5.01)	(-5.25; 13.75)	5.3 (2.85)	(-0.15; 10.65)
3h30min	6.6 (3.61)	(-0.21; 13.46)	5.1 (4.92)	(-4.19; 14.44)	3.6 (3.45)	(-2.92; 10.17)
4h	5.5 (4.57)	(-3.15; 14.15)	-2.6 (4.46)	(-11.23; 6.09)	0.5 (2.99)	(-5.16; 6.16)
6h	8.1 (4.79)	(-0.96; 17.21)	-1.1 (9.00)	(-18.63; 16.35)	3.9 (4.33)	(-4.33; 12.08)
12h	4.0 (2.12)	(-0.02; 8.02)	4.8 (1.68)	(1.57; 7.93)	8.9 (1.87)	(5.22; 12.49)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment Arm: IR Paliperidone
Sex: Male

	Day 2 (PALI 4 mg)		Day 3 (PALI 6 mg)		Day 4 (PALI 8 mg)	
	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Time						
Predose	0.6 (1.37)	(-1.76; 2.88)	-0.6 (1.44)	(-3.02; 1.84)	0.7 (1.43)	(-1.68; 3.15)
30min	3.7 (1.95)	(0.42; 7.02)	2.4 (1.66)	(-0.38; 5.21)	5.6 (1.76)	(2.61; 8.56)
1h	5.0 (1.73)	(2.10; 7.95)	5.7 (1.63)	(2.95; 8.44)	6.6 (1.62)	(3.90; 9.38)
1h30min	10.6 (2.00)	(7.26; 14.02)	7.6 (1.86)	(4.49; 10.79)	11.6 (2.20)	(7.89; 15.33)
2h	6.3 (1.65)	(3.49; 9.07)	5.7 (2.11)	(2.15; 9.29)	8.0 (1.88)	(4.82; 11.18)
2h30min	3.6 (1.45)	(1.14; 6.03)	4.1 (1.29)	(1.88; 6.23)	5.6 (1.62)	(2.87; 8.35)
3h	3.9 (1.72)	(0.95; 6.77)	3.7 (1.69)	(0.84; 6.55)	7.7 (2.29)	(3.83; 11.59)
3h30min	3.6 (1.58)	(0.97; 6.30)	0.9 (1.70)	(-1.99; 3.76)	5.0 (1.49)	(2.51; 7.54)
4h	3.0 (1.79)	(-0.05; 5.99)	3.1 (1.72)	(0.20; 6.02)	4.4 (1.68)	(1.58; 7.26)
6h	2.5 (1.89)	(-0.72; 5.67)	-0.3 (1.96)	(-3.59; 3.04)	2.4 (1.64)	(-0.33; 5.22)
12h	2.1 (1.41)	(-0.26; 4.49)	-1.1 (1.63)	(-3.87; 1.64)	1.2 (1.72)	(-1.68; 4.14)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment Arm: IR Paliperidone
Sex: Male

	Day 8 (PALI 8 mg)		Day 9 (Posttreatment)		Day 10 (Posttreatment)	
	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Time						
Predose	1.9 (1.69)	(-0.96; 4.78)	1.5 (2.18)	(-2.20; 5.17)	-0.3 (1.60)	(-3.02; 2.42)
30min	6.5 (1.83)	(3.44; 9.62)	5.5 (1.90)	(2.29; 8.71)	6.6 (1.76)	(3.61; 9.56)
1h	8.5 (1.60)	(5.79; 11.21)	5.4 (1.80)	(2.35; 8.43)	2.0 (1.92)	(-1.27; 5.22)
1h30min	11.5 (1.88)	(8.33; 14.67)	5.3 (2.45)	(1.17; 9.44)	2.3 (2.49)	(-1.87; 6.54)
2h	9.4 (1.53)	(6.81; 11.97)	5.2 (1.97)	(1.87; 8.52)	0.8 (2.08)	(-2.70; 4.31)
2h30min	7.8 (1.58)	(5.16; 10.49)	0.9 (1.88)	(-2.31; 4.03)	-0.9 (1.64)	(-3.69; 1.85)
3h	7.4 (1.76)	(4.44; 10.40)	2.0 (1.64)	(-0.76; 4.76)	-0.4 (1.83)	(-3.46; 2.73)
3h30min	4.7 (2.22)	(0.98; 8.47)	3.2 (1.78)	(0.22; 6.23)	0.3 (1.55)	(-2.34; 2.89)
4h	5.6 (1.50)	(3.07; 8.15)	1.3 (1.43)	(-1.14; 3.69)	1.8 (1.79)	(-1.19; 4.86)
6h	5.2 (1.73)	(2.30; 8.14)	2.0 (1.88)	(-1.15; 5.21)	0.4 (1.72)	(-2.54; 3.26)
12h	4.0 (1.47)	(1.51; 6.49)	4.1 (1.68)	(1.25; 6.93)	3.0 (1.73)	(0.04; 5.90)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment Arm: IR Paliperidone
Sex: Female

	Day 2 (PALI 4 mg)		Day 3 (PALI 6 mg)		Day 4 (PALI 8 mg)	
	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Time						
Predose	4.8 (2.97)	(-0.87; 10.37)	4.3 (2.94)	(-1.32; 9.82)	2.9 (3.10)	(-2.99; 8.74)
30min	6.3 (1.87)	(2.56; 10.11)	2.0 (3.06)	(-3.95; 7.95)	3.1 (3.98)	(-4.60; 10.89)
1h	4.8 (3.94)	(-2.71; 12.21)	-0.3 (5.01)	(-9.73; 9.23)	3.0 (3.20)	(-3.07; 9.07)
1h30min	2.1 (3.07)	(-3.82; 8.10)	0.4 (4.32)	(-7.80; 8.55)	1.6 (3.96)	(-5.88; 9.13)
2h	1.1 (2.74)	(-4.18; 6.46)	0.1 (2.66)	(-4.91; 5.16)	6.5 (3.95)	(-0.98; 13.98)
2h30min	0.8 (3.36)	(-5.62; 7.12)	3.0 (3.67)	(-3.96; 9.96)	-0.3 (4.98)	(-9.97; 9.40)
3h	3.1 (3.06)	(-2.66; 8.91)	-3.1 (3.29)	(-9.35; 3.10)	2.1 (4.55)	(-6.70; 10.98)
3h30min	0.9 (3.21)	(-5.21; 6.96)	-4.1 (2.08)	(-8.07; -0.18)	-5.1 (3.94)	(-12.80; 2.52)
4h	2.1 (3.40)	(-4.32; 8.57)	-1.6 (2.52)	(-6.40; 3.15)	-3.0 (4.48)	(-11.70; 5.70)
6h	3.6 (5.89)	(-7.53; 14.78)	-3.3 (5.07)	(-12.86; 6.36)	1.4 (5.65)	(-9.33; 12.08)
12h	2.0 (2.20)	(-2.16; 6.16)	-0.1 (2.75)	(-5.34; 5.09)	2.5 (2.56)	(-2.36; 7.36)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment Arm: IR Paliperidone
Sex: Female

	Day 8 (PALI 8 mg)		Day 9 (Posttreatment)		Day 10 (Posttreatment)	
	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Time						
Predose	7.4 (3.78)	(0.21; 14.54)	7.4 (3.74)	(0.30; 14.45)	5.0 (2.43)	(0.40; 9.60)
30min	8.4 (3.01)	(2.57; 14.29)	1.4 (3.77)	(-5.90; 8.76)	8.1 (5.43)	(-2.40; 18.69)
1h	10.3 (4.21)	(2.27; 18.23)	0.5 (4.05)	(-7.17; 8.17)	1.9 (4.29)	(-6.26; 10.01)
1h30min	7.5 (4.35)	(-0.75; 15.75)	3.0 (4.17)	(-4.91; 10.91)	1.1 (3.80)	(-6.07; 8.32)
2h	8.4 (3.69)	(1.39; 15.36)	3.4 (3.40)	(-3.18; 10.04)	2.5 (1.61)	(-0.56; 5.56)
2h30min	8.8 (4.18)	(0.83; 16.67)	2.0 (3.62)	(-4.85; 8.85)	1.6 (3.41)	(-4.83; 8.08)
3h	6.6 (5.34)	(-3.50; 16.75)	4.3 (5.13)	(-5.47; 13.97)	4.9 (3.08)	(-0.96; 10.71)
3h30min	7.3 (3.75)	(0.15; 14.35)	5.3 (5.21)	(-4.63; 15.13)	3.1 (3.68)	(-3.85; 10.10)
4h	6.1 (4.42)	(-2.25; 14.50)	-2.7 (4.50)	(-11.46; 6.03)	0.3 (3.12)	(-5.66; 6.16)
6h	9.3 (4.85)	(0.07; 18.43)	-0.4 (9.67)	(-19.22; 18.36)	4.0 (4.56)	(-4.64; 12.64)
12h	4.3 (2.20)	(0.08; 8.42)	5.8 (1.45)	(3.01; 8.49)	9.9 (2.02)	(5.94; 13.78)

Best Possible Copy

The following is a copy of sections of summary tables provided in the 6/29/06 e-mail showing only the Pal group least square mean changes in QTcF (previous tables showed raw group mean changes) subdivided by gender for post-dose time-points during treatment days corresponding to Table 109 of the CSR (Table 109 was also shown in Section 7.1.12 of the review of the NDA which only included results of QTcLD and not for other QTc results such as QTcF and QTlc).

Note gender differences in the tables below. While males appeared to show a slightly numerically greater peak mean increase in QTc than females (examine the 1 ½ hour post-dose time-points on Days 2, 4 and 8), females appeared to show a more sustained QTc prolongation effect than males (examine Day 8 pre-dose values and values at subsequent time points for each gender). Results of QTcLD are not shown but were generally similar to results of QTcF shown below.

Table ECG.06C: Least Square Mean Differences from Day 1 on Days 2, 3, 4, 8, 9 and 10 at Each Time Point by Sex While Adjusting for Other Potential Confounding Factors (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment: IR Paliperidone
Sex: Male

	Day 2		Day 3		Day 4	
Time	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)
Predose	0.2 (2.42)	(-3.86; 4.17)	-1.0 (2.42)	(-5.01; 3.02)	0.3 (2.42)	(-3.69; 4.35)
30min	3.2 (2.39)	(-0.82; 7.12)	1.8 (2.39)	(-2.12; 5.82)	5.0 (2.39)	(1.04; 8.98)
1h	4.5 (2.39)	(0.49; 8.43)	5.1 (2.39)	(1.15; 9.09)	6.1 (2.39)	(2.10; 10.04)
1h30min	10.1 (2.39)	(6.10; 14.04)	7.1 (2.39)	(3.10; 11.04)	11.0 (2.39)	(7.07; 15.01)
2h	5.7 (2.39)	(1.74; 9.68)	5.2 (2.39)	(1.18; 9.12)	7.4 (2.39)	(3.46; 11.40)
2h30min	3.0 (2.39)	(-0.96; 6.98)	3.5 (2.39)	(-0.48; 7.45)	5.0 (2.39)	(1.07; 9.01)
3h	3.3 (2.39)	(-0.68; 7.26)	3.1 (2.39)	(-0.85; 7.09)	7.2 (2.41)	(3.18; 11.16)
3h30min	3.1 (2.39)	(-0.90; 7.04)	0.3 (2.39)	(-3.65; 4.29)	4.5 (2.39)	(0.49; 8.43)
4h	2.4 (2.39)	(-1.57; 6.37)	2.5 (2.39)	(-1.43; 6.51)	3.8 (2.39)	(-0.12; 7.82)
6h	1.9 (2.39)	(-2.07; 5.87)	-0.8 (2.39)	(-4.82; 3.12)	1.9 (2.39)	(-2.10; 5.84)
12h	1.7 (2.41)	(-2.32; 5.67)	-1.8 (2.42)	(-5.80; 2.24)	0.8 (2.41)	(-3.21; 4.78)

See footnotes on the first page of the table.

Table ECG.06C: Least Square Mean Differences from Day 1 on Days 2, 3, 4, 8, 9 and 10 at Each Time Point by Sex While Adjusting for Other Potential Confounding Factors (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment: IR Paliperidone
Sex: Male

	Day 8		Day 9		Day 10	
Time	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)
Predose	1.5 (2.42)	(-2.51; 5.52)	1.1 (2.44)	(-2.96; 5.12)	-0.7 (2.44)	(-4.75; 3.33)
30min	6.0 (2.39)	(1.99; 9.93)	4.9 (2.39)	(0.96; 8.90)	6.0 (2.39)	(2.04; 9.98)
1h	7.9 (2.39)	(3.96; 11.90)	4.8 (2.39)	(0.85; 8.79)	1.4 (2.39)	(-2.57; 5.37)
1h30min	10.9 (2.39)	(6.96; 14.90)	4.7 (2.39)	(0.77; 8.70)	1.8 (2.39)	(-2.21; 5.73)
2h	8.8 (2.39)	(4.85; 12.79)	4.6 (2.39)	(0.65; 8.59)	0.2 (2.39)	(-3.73; 4.20)
2h30min	7.1 (2.41)	(3.07; 11.05)	0.3 (2.41)	(-3.65; 4.33)	-1.5 (2.39)	(-5.46; 2.48)
3h	6.8 (2.39)	(2.88; 10.82)	1.4 (2.39)	(-2.54; 5.40)	-0.9 (2.39)	(-4.90; 3.04)
3h30min	4.2 (2.39)	(0.18; 8.12)	2.7 (2.39)	(-1.32; 6.62)	-0.3 (2.39)	(-4.26; 3.68)
4h	5.0 (2.39)	(1.07; 9.01)	0.7 (2.39)	(-3.26; 4.68)	1.3 (2.39)	(-2.71; 5.23)
6h	4.7 (2.39)	(0.68; 8.62)	1.5 (2.39)	(-2.51; 5.43)	-0.2 (2.39)	(-4.18; 3.76)
12h	3.6 (2.41)	(-0.43; 7.55)	3.6 (2.42)	(-0.37; 7.66)	2.5 (2.41)	(-1.46; 6.52)

See footnotes on the first page of the table.

Table ECG.06C: Least Square Mean Differences from Day 1 on Days 2, 3, 4, 8, 9 and 10 at Each Time Point by Sex While Adjusting for Other Potential Confounding Factors (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)
Parameter: QTcF (ms)
Treatment: IR Paliperidone
Sex: Female

	Day 2		Day 3		Day 4	
Time	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)
Predose	3.3 (4.19)	(-3.66; 10.18)	2.8 (4.19)	(-4.16; 9.68)	1.4 (4.19)	(-5.53; 8.31)
30min	4.5 (4.62)	(-3.13; 12.11)	-0.5 (4.38)	(-7.71; 6.74)	0.7 (4.38)	(-6.57; 7.89)
1h	3.3 (4.19)	(-3.66; 10.18)	-1.7 (4.19)	(-8.66; 5.18)	1.5 (4.19)	(-5.41; 8.43)
1h30min	1.4 (4.38)	(-5.88; 8.58)	-1.1 (4.19)	(-8.03; 5.81)	0.1 (4.19)	(-6.78; 7.06)
2h	0.4 (4.38)	(-6.88; 7.58)	-1.4 (4.19)	(-8.28; 5.56)	5.0 (4.19)	(-1.91; 11.93)
2h30min	-0.7 (4.19)	(-7.66; 6.18)	1.5 (4.19)	(-5.41; 8.43)	-1.1 (4.38)	(-8.31; 6.15)
3h	1.6 (4.19)	(-5.28; 8.56)	-4.6 (4.19)	(-11.53; 2.31)	1.4 (4.38)	(-5.88; 8.58)
3h30min	-0.6 (4.19)	(-7.53; 6.31)	-5.6 (4.19)	(-12.53; 1.31)	-5.9 (4.38)	(-13.16; 1.29)
4h	0.6 (4.19)	(-6.28; 7.56)	-3.1 (4.19)	(-10.03; 3.81)	-3.8 (4.38)	(-11.02; 3.44)
6h	2.1 (4.19)	(-4.78; 9.06)	-4.7 (4.19)	(-11.66; 2.18)	-0.1 (4.19)	(-7.03; 6.81)
12h	0.5 (4.19)	(-6.41; 7.43)	-1.6 (4.19)	(-8.53; 5.31)	1.0 (4.19)	(-5.91; 7.93)

See footnotes on the first page of the table.

Table ECG.06C: Least Square Mean Differences from Day 1 on Days 2, 3, 4, 8, 9 and 10 at Each Time Point by Sex While Adjusting for Other Potential Confounding Factors (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)
Parameter: QTcF (ms)
Treatment: IR Paliperidone
Sex: Female

	Day 8		Day 9		Day 10	
Time	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)
Predose	5.9 (4.19)	(-1.03; 12.81)	5.9 (4.19)	(-1.03; 12.81)	3.5 (4.19)	(-3.41; 10.43)
30min	5.9 (4.38)	(-1.29; 13.17)	-1.1 (4.38)	(-8.29; 6.17)	5.7 (4.38)	(-1.57; 12.89)
1h	8.8 (4.19)	(1.84; 15.68)	-1.0 (4.19)	(-7.91; 5.93)	0.4 (4.19)	(-6.53; 7.31)
1h30min	6.0 (4.19)	(-0.91; 12.93)	1.5 (4.19)	(-5.41; 8.43)	-0.4 (4.19)	(-7.28; 6.56)
2h	6.9 (4.19)	(-0.03; 13.81)	2.6 (4.38)	(-4.59; 9.86)	1.0 (4.19)	(-5.91; 7.93)
2h30min	7.3 (4.19)	(0.34; 14.18)	0.5 (4.19)	(-6.41; 7.43)	0.1 (4.19)	(-6.78; 7.06)
3h	5.1 (4.19)	(-1.78; 12.06)	2.8 (4.19)	(-4.16; 9.68)	3.4 (4.19)	(-3.53; 10.31)
3h30min	5.8 (4.19)	(-1.16; 12.68)	3.8 (4.19)	(-3.16; 10.68)	1.6 (4.19)	(-5.28; 8.56)
4h	4.6 (4.19)	(-2.28; 11.56)	-3.5 (4.38)	(-10.74; 3.72)	-1.2 (4.19)	(-8.16; 5.68)
6h	7.8 (4.19)	(0.84; 14.68)	-1.2 (4.38)	(-8.45; 6.01)	2.5 (4.19)	(-4.41; 9.43)
12h	2.8 (4.19)	(-4.16; 9.68)	4.3 (4.19)	(-2.66; 11.18)	9.1 (4.38)	(1.84; 16.29)

See footnotes on the first page of the table.

The following tables show QTcF mean changes by treatment day of each of the above gender by treatment groups. Note that females tend to show a slightly greater maximal numerical QTc increase than males (observed on Day 8 of treatment). This gender difference was greater with Moxifloxacin treatment (on Day 8) than with Pal treatment.

Table ECG.05B: ECG: Descriptive statistics on Differences from Day 1 in Day Averaged QT/QTc by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)
Parameter: QTcF (ms)
Sex: Female

Treatment Arm	Visit	Treatment Group	N	Mean (SE)	Mean Difference (SE)	90% Confidence Interval on Mean Difference
IR Paliperidone	Day 1	Placebo	8	402.5 (5.64)		
	Day 2	Pali 4mg IR q.d.	7	407.3 (6.38)	3.0 (2.77)	(-2.38; 8.38)
	Day 3	Pali 6mg IR q.d.	8	400.9 (5.04)	-1.6 (2.58)	(-6.52; 3.27)
	Day 4	Pali 8mg IR q.d.	7	405.3 (5.48)	1.0 (3.42)	(-5.64; 7.64)
	Day 8	Pali 8mg IR q.d.	8	409.6 (6.31)	7.1 (3.07)	(1.31; 12.94)
	Day 9	Posttreatment	8	405.6 (5.52)	3.1 (4.34)	(-5.09; 11.34)
	Day 10	Posttreatment	8	406.6 (5.32)	4.1 (2.35)	(-0.32; 8.57)
Moxifloxacin	Day 1	Placebo	11	401.4 (4.12)		
	Day 2	Placebo	11	401.6 (3.38)	0.3 (1.22)	(-1.94; 2.49)
	Day 3	Placebo	11	403.2 (3.00)	1.8 (2.49)	(-2.70; 6.34)
	Day 4	Placebo	11	402.5 (2.70)	1.1 (2.22)	(-2.94; 5.12)
	Day 8	MOXI 400 mg	11	411.0 (2.77)	9.6 (2.06)	(5.90; 13.38)
	Day 9	Posttreatment	11	405.2 (2.33)	3.8 (2.38)	(-0.50; 8.14)
	Day 10	Posttreatment	11	402.6 (2.12)	1.3 (2.44)	(-3.15; 5.70)

Table ECG.05B: ECG: Descriptive statistics on Differences from Day 1 in Day Averaged QT/QTc by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)
Parameter: QTcF (ms)
Sex: Male

Treatment Arm	Visit	Treatment Group	N	Mean (SE)	Mean Difference (SE)	90% Confidence Interval on Mean Difference
IR Paliperidone	Day 1	Placebo	36	383.9 (2.43)		
	Day 2	Pali 4mg IR q.d.	36	387.2 (2.41)	3.3 (1.16)	(1.31; 5.24)
	Day 3	Pali 6mg IR q.d.	36	385.1 (2.24)	1.2 (1.29)	(-1.02; 3.35)
	Day 4	Pali 8mg IR q.d.	36	387.5 (2.10)	3.6 (1.08)	(1.75; 5.41)
	Day 8	Pali 8mg IR q.d.	36	389.5 (2.03)	5.6 (1.09)	(3.75; 7.42)
	Day 9	Posttreatment	36	386.9 (2.62)	2.9 (1.28)	(0.75; 5.09)
	Day 10	Posttreatment	36	385.3 (2.33)	1.4 (1.31)	(-0.82; 3.60)
Moxifloxacin	Day 1	Placebo	47	389.3 (2.27)		
	Day 2	Placebo	47	389.2 (2.20)	-0.0 (0.63)	(-1.08; 1.04)
	Day 3	Placebo	47	387.3 (2.12)	-1.9 (0.88)	(-3.42; -0.45)
	Day 4	Placebo	47	387.9 (2.26)	-1.4 (0.99)	(-3.05; 0.28)
	Day 8	MOXI 400 mg	47	392.5 (2.07)	3.3 (1.18)	(1.27; 5.24)
	Day 9	Posttreatment	47	389.6 (1.98)	0.3 (1.11)	(-1.57; 2.17)
	Day 10	Posttreatment	47	387.3 (2.13)	-1.9 (1.19)	(-3.91; 0.08)

It is noteworthy to show results of some individual subject QTcLD values against Pal plasma levels that were found in Attachment 4.3 of the CSR of Study SCH-1009 (found in the original NDA submission). Only a few selected subjects are shown below. Note that some subjects appear to show a lag in peak QTc values several hours after Cmax and may show a secondary increase in QTc values at 12 hours post-dose (it is not clear how high QTc increases after the 6 hour post-dose time-point since only a 12 and 24 hour post-dose assessment was collected thereafter on selected treatment days). Also compare results across treatment days below. While examining these figures, it is also important to note that some apparent changes in QTc

over time could be reflecting test-retest variance in values independent of treatment and plasma levels.

Note that the upper line in the figures corresponds to QTc interval and the lower line shows plasma levels.

Figure PK/PD 25: Individual Paliperidone Plasma Concentration and QTcLD in Function of Time

[R076477-SCH-1009] page 2 of 63

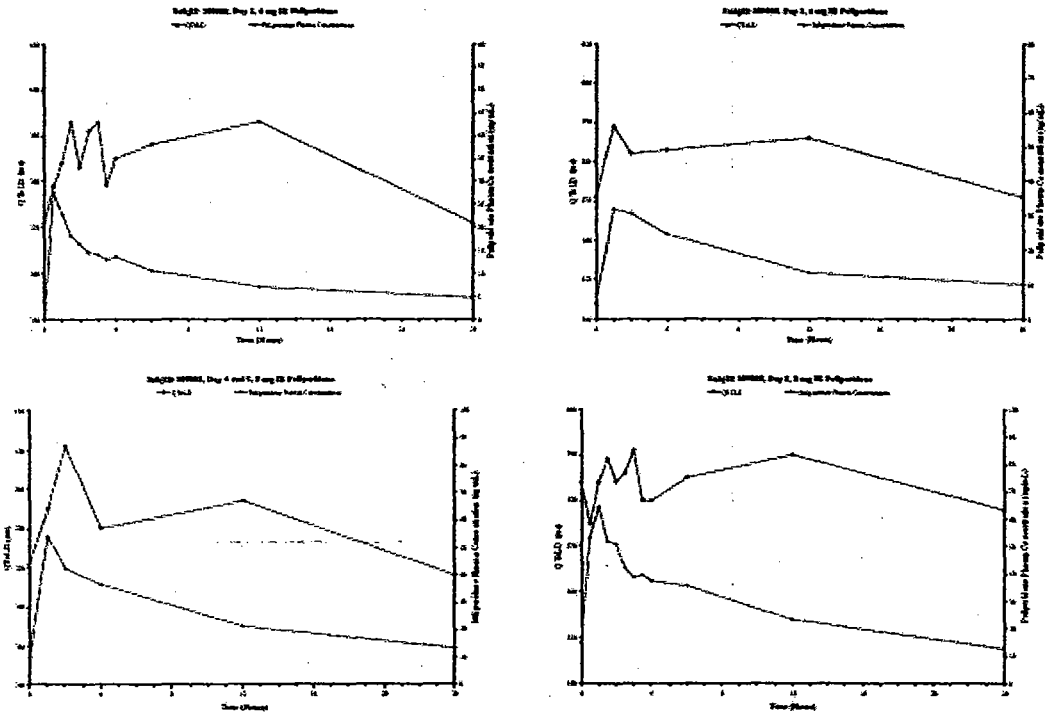


Figure PK/PD 25: Individual Paliperidone Plasma Concentration and QTcLD in Function of Time

[R076477-SCH-1009] page 6 of 63

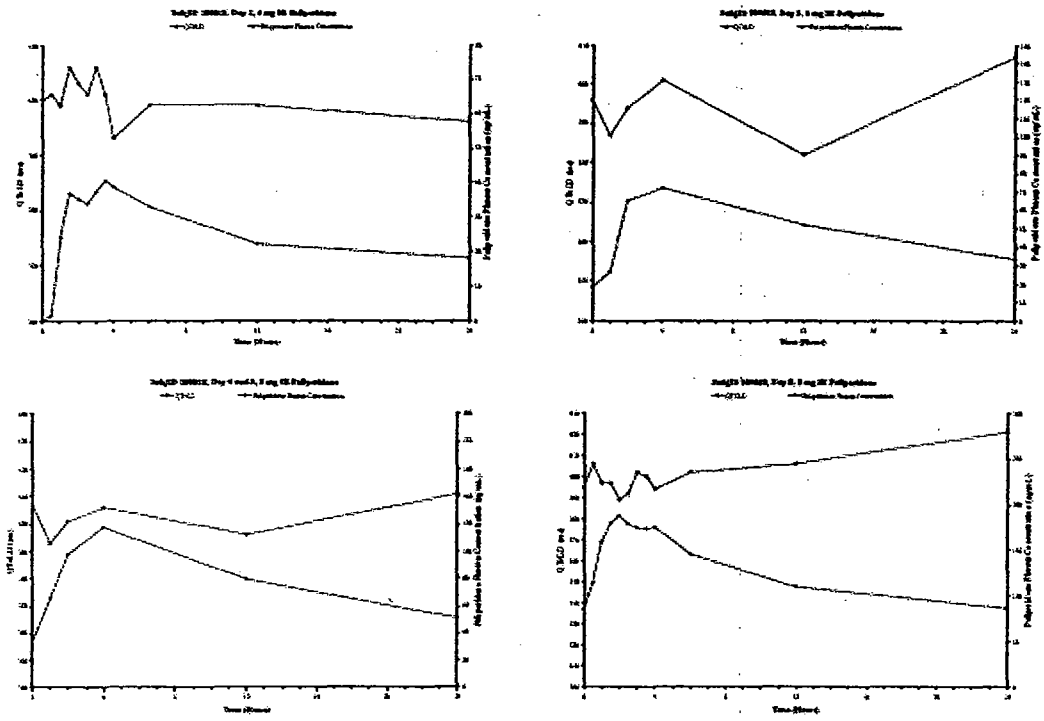
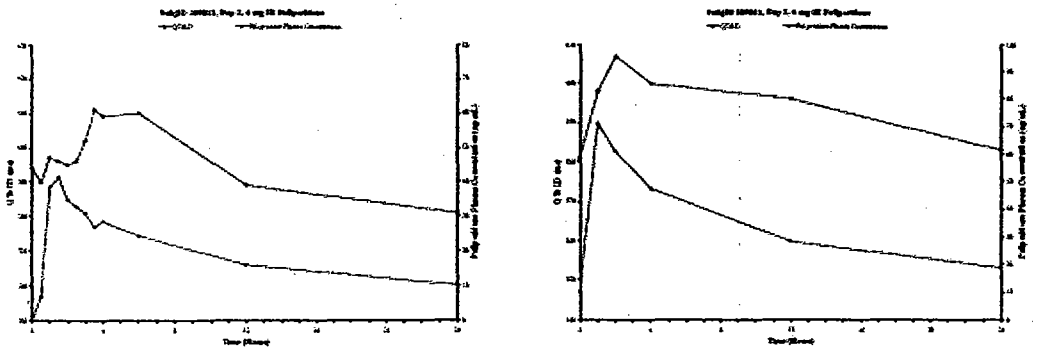
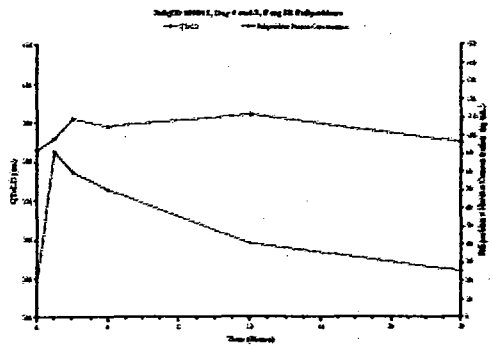
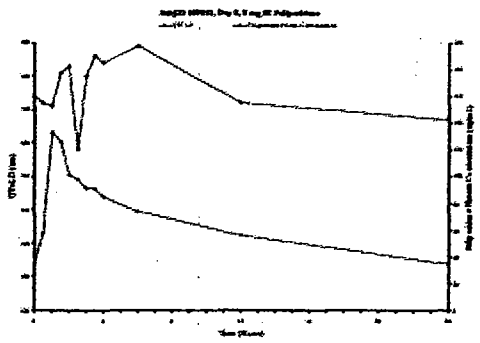


Figure PK/PD 25: Individual Paliperidone Plasma Concentration and QTcLD in Function of Time

[R076477-SCH-1009] page 4 of 63







Reviewer Recommendations. *Given QTc interval prolongation effects (described in the original NDA review), consultative input from the Cardiorenal Division in the Agency will be obtained. Recommendations for questions for the consultant and for information to be provided for the consultant were e-mailed to Dr. Ni Khin on 8/7/06 (upon her 8/7/06 e-mailed request). These recommendations are copied in Attachment 2 of this review. OCPB input on questions and on information to provide for the consultant was also recommended with respect to PK and PK-pharmacodynamic relationships (specifically regarding effects on the cardiovascular system).*

VI. 7/15/06-Response to 6/28/06-Question 2 on the Phase III Formulation

The sponsor was asked to verify if all Phase III trials used the [redacted] formulation [redacted] The sponsor indicated that trials used 3 and 9 mg F016 and F017 formulations, respectively. These formulations differed [redacted] by only the absence of color coating, printing excipients and "minor adjustments" in the amount of other "excipients" (e.g. polyethylene glycol and others). The sponsor provided additional CMC related information on the quantitative composition of Phase III formulations in their 7/15/06 e-mailed response (the corresponding NDA amendment submission is pending at this time).

Reviewer Comment and Recommendations
It appears that there were minor differences, according to the sponsor's overall explanation. However, since the information is CMC related and some of the differences could impact on PK, it is recommended that input from CMC and OCPB be obtained (it is recommended that these consultants be provided with their 7/15/06 response and asked if these minor differences are a significant CMC or OCPB related concern).

VII. 7/21/06 Response to 6/28/06 Question 3 on a Subject with Syncope and "Pauses" on Holter Monitoring and on a Young Female Subject who Suddenly Died in an Open-Label Extension Study (Subjects 300541 and 100963).

The above subjects were described in the review of the original NDA in Section 7. The sponsor was asked to provide more information in these subjects. Subject 100963 was found by the

undersigned reviewer in a Safety Alert Report submitted under the OROS Pal IND (as previously described in the original review).

Reviewer Comments

Little new information on the above subjects could be found in the sponsor's response (see Attachment 3 of this review sent in a 7/21/06 e-mail from the sponsor of which the NDA amendment submission is pending at this time). The information provided in their response does not change the undersigned reviewer's conclusion that events are suspicious of a drug-related etiology and considered to be likely (in the absence of any clear or probable non-drug-related etiology). Refer to the original NDA review for additional comments about these individual subjects and for recommendations. A few additional comments relevant to potential etiologies are made below based on the information in their response.

Subject 300541

Subject 300541 (had syncope, pauses on holter monitoring and other events including AEs leading to an ADO and SAEs, as provided in the original NDA review). The verbatim term syncope was reported as an AE, but the nature and description of "syncope" could not be found in the sponsor's response. The subject was also reported to have events of fainting and dizziness. Refer to Attachment 3 for details on this subject.

The following are reviewer comments that were not previously provided in the original NDA review and are based on the sponsor's response.

It appears that concomitant lorazepam probably played little to no a role in the adverse events in this subject for the following reasons. Lorazepam was last given on Day 4 and adverse events first occurred on Day 5, with additional events occurring on Day 6. Furthermore these events resolved within 2-4 days of Pal treatment cessation.

Vital signs and ECG assessments results on Day 5 of 12 mg Pal treatment (when fainting, hypotension, syncope and other events were reported) could not be found in the sponsor's response. Therefore, the onset of bradycardia and sinus pauses reported on Day 6 could have occurred sooner. Furthermore, bradycardia and sinus pauses could explain the AEs that reported on Day 5.

Although anterior fascicular block found at baseline could have played a role are suggested in underlying condition in this subject, the subject was not reported to have any past history or cardiac disorders are events similar to those observed during paliperidone treatment (e.g. no history of hypotensive episodes, fainting, sinus pauses, heart rates lower than 60 and as low as 38 bpm as were reported on Day 6). Additionally, resolution of the events after cessation of pal treatment together with the nature of the events, as well as the timing of events relative to treatment onset are consistent with at least a major role of Pal treatment.

Subject was reported as an ADO due to "exacerbation of psychosis" on Day 6 and Pal treatment was discontinued on Day 5 for this reason, rather than due to SAEs and other cardiovascular system adverse events (e.g. syncope, hypotension, among others). The sponsor provided the

following additional information with respect to the reason for discontinuation as follows (copied from their response):

NOTE The following description is included because this subject's reason for discontinuation differed from the process described later in the document:
The subject was discontinued due to the adverse event of "exacerbation of psychosis", described as not related by the investigator. During the investigator meeting investigators were trained about what to do in the event a subject had an exacerbation of symptoms associated with their underlying schizophrenia diagnosis. They were instructed to differentiate between symptoms caused by the disease and those potentially caused by the drug. If in their clinical judgment the symptoms were caused by the disease (e.g. were consistent with past exacerbations) and were thus a result of the drug not working (e.g. lack of efficacy), they were to indicate the reason for withdrawal as "lack of efficacy". If their clinical judgment was that the drug was causing the symptoms, they were instructed to list the reason for withdrawal as the adverse event of exacerbation. While these instructions would have suggested this subject should have been discontinued due to "lack of efficacy", it is ultimately up to the investigator to select the reason for discontinuation.

See recommendations below.

Subject 100963

See Attachment 3 of this review for details on this 23 year old female who suddenly died after week 16 of 12 mg daily Pal during an OL extension trial (Study -701). Little new information was provided. However, the sponsor's response specified that trihexyphenidyl 2 mg was prescribed for EPS (this drug was given on the day preceding her death). Information on starting date and treatment regimen could not be found, although this subject had no evidence of EPS on her last study visit.

As previously described in the review of the original NDA, her death occurred about one month after she was last seen at a scheduled study visit during OL treatment of 12 mg Pal/day. She did not show up for her next study visit and had developed AEs 2 days later followed by death on the day after her initial reported symptoms.

In the absence of any clear etiology or risk factors (bronchospam or pulmonary embolism were considered in the differential diagnosis and the subject was a nonsmoker) or underlying conditions (no concomitant illnesses could be found in narrative descriptions), Pal treatment is highly suspected to be involved with events leading to death in this subject.

Although this subject had already received Pal treatment for months adverse effects of pal (including QT prolongation, cardiovascular effects, among others) are described in chronically treated subjects (as described in the original NDA review). Furthermore, limitations with the OL longterm safety data are inherent in the ability to detect potential safety signals (e.g. the absence of a placebo group is a major limitation, refer to the original NDA review for more examples and further discussion).

Reviewer Recommendations

It is recommended that events in subject 300541 and 100963 be described under [redacted]

NDA review) under Warning and Precautions in labeling. A description of subject 100963 is recommended for these subsections since a role of cardiovascular and ECG effects cannot be ruled out and could at least contribute to events that ensued in this subject. A summary of the events of this subject should also be included under the Seizures section in proposed labeling, since the subject appeared to have a seizure. Also consider describing the events of this subject under the "Dysphagia" subsection of labeling, while noting that the subject vomited prior to an episode suggestive of seizure. In any case a differential diagnosis (as described by the undersigned reviewer in the original NDA review) should be included in the description in labeling, as well as a comment that events leading to death and the cause of death remains unclear, as well as noting that no autopsy was performed on this subject.

Given the explanation on the reason for discontinuation of Pal treatment and early study withdraw provided in the sponsor's response (as previously shown in this review) the following concern should be considered. It is not clear if there are additional subjects with clinically remarkable events concurrent with an ADO due to "exacerbation of schizophrenia" that could be drug-related and involving another organ system (e.g. the cardiovascular system). It is recommended that this issue be resolved before granting a final approval on this NDA and that the methodology for AE reporting be included in labeling. Consider asking the sponsor if there are any other Pal subjects in the Phase III short-term double-blind trials with "exacerbation of schizophrenia" reported as an ADO who had concurrent remarkable clinical events (reported as SAEs, ADOs, or as meeting clinically remarkable outlier criteria). If so, then it is recommended that the sponsor provide a line listing of these subjects that includes the following information: subject number, verbatim and preferred ADO, SAE and AE terms, the value of any clinical parameter that met outlier criteria, and a hyperlink to a narrative description (that is included in the submission).

Another concern regarding reporting methods for reporting "lack-of-efficacy" versus "exacerbation of schizophrenia" (as previously described) on results on disposition under the "lack-of-efficacy" and it's potential relevance to assessing the efficacy of the drug. In the case of the subject above, it is reasonable to consider that any psychotic symptoms in the first several days of treatment would not be due to a lack-of-efficacy since treatment was only recently initiated. However, such subjects later in treatment (over at least the final 3-4 weeks of treatment) may not be as easily distinguishable. This issue should be resolved before granting a final approval action on this NDA. In addition to the sponsor providing a response to this potential issue, consider asking for the incidence of early withdrawals due to" lack-of-efficacy" and the incidence of ADOs due to "exacerbation of schizophrenia" for each treatment week of the 6-week DB phase of the short-term Phase III safety dataset (Studies -303, 304 and 305, combined) and to identify and describe any ADOs due to this reason that also had adverse events

(that were not related to symptoms at the time of the ADO, such as cardiovascular related AEs, extrapyramidal side effects or others), abnormal clinical measures or clinical abnormalities during the time or just before the onset of symptoms leading to the ADO of exacerbation of schizophrenia. The sponsor could also be asked to provide the investigator's rationale for reporting each of these ADO as an "exacerbation of the disorder" rather than as "lack-of-efficacy." This may require that the sponsor contact the investigator if they do not already have this information.

VIII. 7/26/06-Response to 6/28/06-Questions 4 and 5 on Selected Subjects

The sponsor was asked the following question (Question 4) and responded in a 6/2/06 e-mail

4. **FDA Comment - The following paliperidone subjects are some examples which lead us to wondering if we are missing subjects who were adverse dropouts (ADOs), such as subjects who withdrew from the study for reasons related to AEs or due to clinical abnormalities (e.g. subjects who withdrew consent due to AEs, subjects who were withdrawn due to noncompliance in which their noncompliance was due to AEs or subjects that withdrew early for other reasons related to AEs)?**

Sponsor's Response to Question 4 and Reviewer Comments.
It appears that the sponsor did not provide any new information on individual subjects that were provided for them as examples as subjects that lead to our overall question, copied above. An example of how the sponsor responded is provided below (copied from their response regarding one of the subjects we identified as an example).

a. **FDA Comment** - Subject 503018: This subject cannot be found in line listings of SAEs or ADOs. The narrative indicates that the elevations in LFTs were not reported as AEs. Please clarify and provide the rationale for how events of elevated LFTs were actually reported in subjects and clarify why the drug was stopped and why the subject was noncompliant.

J&JPRD Response - Subject 503018 (SCH-305) was randomized to receive paliperidone ER 15 mg/day. When clarification was sought from the site to assist in this response, the investigator recently provided the following explanation regarding elevations in AST (154 U/L), ALT (323 U/L) and GGT (175 U/L) observed in the laboratory assessments obtained on Day 15 of the study. The subject was discharged from the hospital on day 15 and continued to receive medication. After reviewing the laboratory results of the sampling on Day 15, the investigator referred the subject to his primary care provider (PCP) who repeated the tests at a local laboratory on Day 18. The PCP instructed the subject to stop taking the study drug at that time. The results from the local laboratory demonstrated a normal AST 25 IU/L (normal range 0-40 IU/L) and still elevated, but lower, ALT of 91 IU/L (normal range 0-40 IU/L) on Day 18. GGT was not included in the panel. The primary care provider believed the LFT abnormalities were related to stomach cramps, reported in the subjects medical history at the beginning of the study, reported as an AE on Day 1 and observed by the site in the days prior to the subject's hospital discharge. Other than the AE of abdominal cramps, the investigator reported no other AEs and no SAEs for this subject during the study. The subject presented for his next scheduled visit on Day 23 and informed the site he had not taken the study drug for the past 5 days. Although the site envisioned study continuation, per the protocol specifications, any subject missing 4 or more consecutive doses must be withdrawn for non-compliance. Therefore, the site withdrew the subject due to "non-compliance".

Additional Reviewer Comments and Recommendations
It is not clear why the above subject was noncompliant and if the subject had been asked why they were noncompliant and if this type of information was being recorded by the investigator. It is also not clear if subjects that withdrew consent or became noncompliant or did not return (and

so dropped out), among other early withdrawals (not reported as ADOs) were asked why. It is also not clear if this information was recorded.

Direct inquiry to the patient about their reasons for becoming noncompliant or withdrawing consent (as examples) might reveal that their early withdraw was due to a potential drug-related reasons (e.g. a given subject could have been feeling sick due to elevations in liver function tests or became non-compliant because of their elevated liver function tests and they were also concerned that continuing treatment could lead to further elevations).

The sponsor did not appear to conduct an inquiry of the investigator and/or subjects as to why the subjects withdrew early (e.g. withdrew consent or became noncompliant) for at least the subjects we identified as examples of subjects that also developed AEs or clinical abnormalities just before and during the time of their early withdraw from the study.

The sponsor also did not appear to conduct a search for additional subjects similar to the examples that were provided for them (e.g. search for subjects who withdrew consent or became noncompliant or withdrew for unspecified or unclear reasons who had AEs or other clinical abnormalities when they withdrew or required treatment for clinical abnormalities when they withdrew).

Some of these patients may have been severely psychotic to the extent that communication with them may have been difficult but it is not clear from the narrative information on these subjects if this was the case. A follow-up inquiry of these subjects might be revealing if the given subject eventually improved enough to be able to communicate adequately. Inquiry of the investigator might also be revealing.

Response to Question 5 and Reviewer Comments
The sponsor was also asked the following question which was the main part of Question 5 in the 6/28/06 e-mail sent to the sponsor (refer to the DFS communications document dated 8/2/06 in DFS for specific communications with the sponsor).

b. **FDA Comment** - Are there any other SAEs that occurred after treatment cessation that were preceded by AEs that led to the SAE that were not captured in the Phase III database (of double-blind and open-label drugs)?

The following example leading to the above question was provided and is provided in this review given the serious nature of the AEs in this subject.

e. **FDA Comment** - Subject 100057: This subject is recorded on the narrative summary table as only having an SAE and is not checked off as being an adverse dropout but is checked off as an SAE (see the "premature discontinued" column on page 1773)? Please clarify why this subject was not considered an ADO.

J&JPRD Response - Subject 100057 (SCH-301) experienced the non-serious adverse events verbatim "restlessness (akathisia)" on Day 4 and "EPS symptoms: muscle stiffness in the entire body" on Day 15 and was treated with benztropine beginning on Day 15. On Day 20 the subject was discharged from the hospital, as allowed by the protocol, and returned for a study visit on Day 22 reporting side effects he "could not tolerate" (restlessness and inability to sleep). The subject was withdrawn from the study and despite the presence of continued adverse events the reason listed by the investigator was subject choice. This investigator designation of reason withdrawn determines who is included in the discontinuation due to adverse events category. On Day 22 the subject had laboratory samples taken and body temperature was recorded as 36.4c. The results of the laboratory samples were reported to the investigative site 2 days later, containing an elevated creatine kinase of 2201 U/L. The subject was contacted and instructed to go to the emergency room immediately, but he did not agree to go until the following day. He was diagnosed with neuroleptic malignant syndrome and elevated creatine kinase. On Day 25 the CK elevation reportedly persisted, but the NMS was considered recovered without sequelae.

The serious adverse event of neuroleptic malignant syndrome was reported by the site as beginning 3 days after the subject was withdrawn from the study (subject's final date in the

R076477-SCH-301 study was the date of withdrawal). Additionally, the event was initially incorrectly identified as occurring in the open label extension phase of the study (R076477-SCH-701). This error was discovered during the data reconciliation process, at which time discussions with the site were held. The site maintained that the start date of the event was after the subject was discontinued from study SCH-301 (as that was when the laboratory values were available and the diagnosis was made) so this date was maintained in the database. As a rule, data for all subjects from their respective study start date through their study end date are summarized. For this subject the reported event occurred after the subject's study end date, thus this event was not included in the summaries. Because this event was recorded as occurring post study, the reason for discontinuation was not queried and the subject was not included in the list of discontinuations due to adverse events, however given the potential clinical importance of the event, a description was included in the submission documents (e.g. 120 day safety update subject narratives).

The sponsor provided the following response to the above question about whether there were other subjects in response to question 5.

To evaluate the question of whether there were other SAEs occurring after subjects discontinued the study that were preceded by AEs potentially leading to the SAE, a review of the clinical and pharmacovigilance databases was performed for Studies R076477-SCH-301, SCH-302, SCH-303, SCH-304, SCH-305, SCH-701, SCH-702, SCH-703, SCH-704, and SCH-705. All SAEs occurring after a subject discontinued the study were reviewed and are included in Attachment 1. These events are divided into those reported only in the pharmacovigilance database (e.g. reported to the company via a CIOMS form) and those found in both the clinical and pharmacovigilance database (e.g. reported to the company via both a CRF page and a CIOMS form). The table was populated with information from the CIOMS reports, patient profiles and previously submitted written narratives. It includes the date and reason a subject discontinued, the date and description of the SAE occurring after discontinuation, and a description and dates for all AEs reported during that study.

The sponsor found only one additional subject (subject 501411) who had the "persisting AE of agitation" who discontinued "due tot lack of efficacy" but later had the SAE of schizophrenia reported at post-study.

Attachment 1 is a listing of subjects with SAEs reported on a date that followed the day of premature study discontinuation in subjects in Phase III trials (this list included subjects who withdrew early due to a variety of reasons such as the withdraw of consent, lack-of-efficacy, ADO's, among others). Most SAE's that occurred after study discontinuation were SAEs of schizophrenia or other psychiatric-related events that appeared to be primarily associated with discontinuation of treatment or lack-of-efficacy or related to their psychiatric condition (based on the timing of these SAEs relative to the timing of treatment discontinuation and by the nature and/or the timing of AE's or ADOs that preceded the post-study SAEs). Other post-study SAEs occurred in placebo subjects. Some subjects had adverse events that began at baseline or resolved prior to study discontinuation or resolved prior to the date of the post- study SAE.

The following additional subject was found by the undersigned reviewer in the sponsor's listing (Attachment 1 of their response):

*Subject 200710 had to **AEs of pneumonia and hydrothorax leading to discontinuation on Day 40 of paliperidone treatment after the dose was recently increased** on Day 36 (from 6 mg daily to 9 mg daily). According to the line-listing hypotension was also reported as an AE on Day 40 ("there were no blood pressure values available for this day," according to that described in the narrative). The hypotension resolved in two days. The AEs of **hydrothorax and pneumonia***

were upgraded to SAEs on Day 44 when the subject was admitted to a general hospital *for treatment of her condition. Treatment included furosemide, an antibiotic, and other medications. Her condition resolved by Day 63 when the subject was discharged from the general hospital. This subject had a history of arteriosclerosis (cardiac and cerebral), QTc prolongation, and intraventricular conduction defect. The timing of the onset of the AE's relative to a recent increase in the dose of paliperidone is suspicious of a role of Pal at least in initial events leading to the more serious complications of hydrothorax and pneumonia), as discussed in more detail below. This female subject also had multiple risk factors for these type of events since she was elderly (65 years old) with concomitant conditions as previously described. Therefore, potential effects of Pal may have played a role together with her pre-existing conditions and risk factors.*

Hemodynamic effects of paliperidone were previously described in the review of NDA 2199. These effects could play a role in subsequent complications in patients with underlying concomitant illnesses and/or risk factors, such as in the above-described subject and in other subjects described in the review of the original NDA.

The incidence of respiratory infection was reported in 3.5% of subjects in the 15 mg paliperidone group to 0.6% of subjects in the placebo group in the primarily non-elderly Phase 3 trials (pooled dataset). Refer to approved Risperdal® labeling for a similar safety signal. Patients, such as the above patient who was elderly with a pre-existing arteriosclerotic disease, are more likely to develop more serious complications due to a less severe Pal-induced AE.

In light of the above comments, it is noteworthy that subject 200214 died of bronchopneumonia in an OL extension trial (a 70 year old male subject). This subject had multiple major medical conditions and complications such that it is difficult to determine whether or not Paliperidone treatment played a role (based on the information provided in the narrative and as described in the review of the original NDA which includes a copy of the narrative).

A few additional SAEs/ADOs were due to respiratory related events in Phase III trials, as described in the review of the original NDA.

The following is a final comment about this additional subject found in the sponsor's listing that was provided in response to question 5 and the potential concern that this subject was not adequately captured in the information found in the original NDA submission. Despite that SAEs were not reported until after treatment cessation and were not found in line listing of SAEs in open-label trials in the original NDA submission, these adverse events were still captured as AE's leading to early discontinuation (and in the sponsor's line listing for ADO's in the original NDA 21999 submission).

Reviewer Recommendations*: the above described subject provides further support for recommendations provided in the review of the original NDA 21999, regarding a lower dose and a more gradual dose increase to be employed in elderly patients and in patients with concomitant illnesses. Given the hemodynamic as well as EKG-related effects of paliperidone described in the original review of NDA 21999 patients with concomitant illnesses involving the*

cardiovascular system may be a particular risk for these drug effects in contributing the development of more serious medical complications (e.g. angina, or other complications as observed in the above subject). In turn, less serious adverse events (e.g. AE's of respiratory infection) associated with paliperidone may pose a greater risk for more serious events (e.g. pneumonia) in some patients, such as the patient described above. The risk for pneumonia should also be addressed under Warnings/Precautions in sections relevant to the elderly and to patients with concomitant illnesses.

IX. A Review of New Information Provided in Narratives of 15 Subjects Provided in the 210-Day Safety Update Report

The 210-Day Safety Update report (SUR) included narratives of 15 subjects in ongoing open label trials that had been previously provided in the four-month safety update report submission under this NDA. Information was added to these narratives in the more recent 210-Day SUR, was primarily of additional SAEs reported in subjects that were previously reported to have other SAEs or ADOs or elevated liver function tests. Most of the added SAEs were psychiatric related events that were typically schizophrenia-related or other psychiatric symptoms that are commonly reported in this patient population. Other newly reported SAEs did not reveal any unexpected drug-related events or involved subjects that were previously described in the review of the original NDA submission in which the added information did not change the overall conclusions. However, the following subject is a possible exception. Subject 500501 was described in the review of the original NDA since this subject developed elevated liver function tests including elevated CPK. The elevated liver function tests were reported as AE's leading to early study withdraw in the original NDA submission. The sponsor has now upgraded these AE's to SAEs. The sponsor explains that this change was made as a result of new information, which provided liver function test values that remained elevated on Day 180 (9 mg/day of paliperidone was discontinued on Day 173) and a further increase in CPK levels of 760 U/l while showing no "evidence of myglobinuria (i.e. positive blood on urine dipstick in the absence of RBC's on microscopy)," and "no evidence of hyperkalemia at any time during the study."

Reviewer Recommendations

The new information provided in the narratives did not reveal any new or unexpected findings that were not previously described in the review of the original NDA submission. However, the additional information on subject 500501 again shows concurrent elevations of CPK with elevations in liver function tests. As previously described the subject had no previous history of liver disease and a non-drug-related etiology could not be identified. Although elevations continued until at least seven days post-treatment cessation it is not uncommon for a drug-induced elevation in liver function tests to lag behind cessation of treatment, among drugs believed to have this adverse effect. Furthermore, paliperidone has a long half-life. Therefore, as previously concluded in the review of the original NDA submission, a potential safety signal for elevations in liver function tests during paliperidone treatment in some subjects is suggested and a may also be associated with elevations in CPK. It is not clear how high liver function test values would have been reached in those subjects who were ADOs due to this adverse event. As

previously recommended, a section under warnings and precautions that describes this potential safety signal is advised for labeling, unless the sponsor can provide convincing evidence that such a potential signal does not exist.

Attachment 1 Narrative descriptions of high CPK outliers

Protocol: R076477-P01-1008; Subject: 100843

Subject 100843 was a white 30-year old male randomized to receive ER OROS paliperidone 15 mg (fasted Phase 3 formulation) during Period 1, 15 mg ER OROS paliperidone (fasted commercial formulation) during Period 2, and 15 mg ER OROS paliperidone (fed commercial formulation) during Period 3. This subject completed all 3 periods of the study.

Cmax levels registered during each treatment period were: period 1: 37.8 ng/mL, period 2: 31.0 ng/mL and period 3: 22.5 ng/mL. The washout period between trial medication administration was 10-14 days.

The laboratory results from the sample obtained at the pre-dose Period 3 visit showed a CK value of 8246 U/L (upper limit of normal 170 U/L in this study) compared to a value of 76 U/L during screening. At the study end the value was 239 U/L. No adverse event was reported regarding this abnormality. The results of the laboratory sample from the pre-dose Period 3 visit also demonstrated elevated ALT and AST values (96 U/L and 215 U/L respectively) compared to values of 32 U/L and 25 U/L respectively, during screening. At study end point values were normalized at 69 U/L and 44 U/L respectively (upper limit of normal 72 and 59 respectively, in this study). This finding of elevated ALT and AST values was reported as a mild, doubtfully related adverse event.

Other adverse events reported around the time of these laboratory abnormalities, included "headache" (2 days after the Period 3 pre-dose assessments) and "sore throat", "night sweats", "nasal congestion" and "dry mouth" (all 3 days after the Period 3 pre-dose assessments).

Given the proximity to these adverse events to the increased CK ALT and AST values, it was likely that all were part of to illness the subject was experiencing at that time. The increase in CK levels at 1 timepoint during the study is thus probably due to other factors than trial medication.

Protocol: R076477-P01-1010; Subject: 101012

Subject 101012 was a black 22-year old male with a medical history of "congenital jaundice hemolytic or hepatic" randomized to receive ER OROS paliperidone 12 mg during Period 1, ER OROS paliperidone 9 mg during Period 2, ER OROS paliperidone 15 mg during Period 3, ER OROS paliperidone 6 mg during Period 4 and ER OROS paliperidone 3 mg during Period 5. This subject completed all 5 periods of the study. The washout in between trial medication administration was at least 9 days.

Cmax levels corresponded to 12.6 ng/mL during period 1, 7.62 ng/mL during period 2, 21.2 ng/mL during period 3, 9.80 ng/mL during period 4 and 3.34 ng/mL during period 5.

The laboratory results form the sample obtained at the pre-dose Period 1 visit demonstrated a CK of 822 U/L (upper limit of normal 545 U/L in this study) compared to 434 U/L during screening. At the pre-dose Period 3 visit the CK was 577 U/L and was reported as a mild, doubtfully related adverse event of "elevated creatine kinase". A re-test the following day had returned to the normal range (263 U/L). At the pre-dose Period 5 visit the CK was 3045 U/L and was reported as a mild doubtfully related adverse event. At the end of the study the CK had returned to the normal range, 433 U/L.

Given the CK abnormality prior to the first dose of ER OROS paliperidone and the return to normal after receiving the highest dose (e.g. pre-dose Period 3 was abnormal and normalized the following day after the 15 mg dose) it is unlikely the paliperidone was causally related to the elevation.

Protocol: R076477-P01-1010; Subject: 101015

Subject 101015 was a white 19-year old male randomized to receive ER OROS paliperidone 6 mg during Period 1, ER OROS paliperidone 3 mg during Period 2, ER OROS paliperidone 9 mg during Period 3, ER OROS paliperidone 15 mg during Period 4 and ER OROS paliperidone 12 mg during Period 5. This subject completed all 5 periods of the study. The washout in between trial medication administration was at least 9 days.

Cmax levels were 13.2 ng/mL in period 1, 2.36 ng/mL during period 2, 12.8 ng/mL during period 3, 27.8 ng/mL during period 4 and 16.3 ng/mL during period 5.

The laboratory results from the sample obtained at the pre-dose Period 5 visit demonstrated a CK of 2885 U/L (upper limit of normal 545 U/L in this study) compared to a value of 222 U/L during screening. A re-test the following day showed a value of 1756 U/L and a value at study end was 1178 U/L. Also at this visit the AST value was elevated to 62 U/L (upper limit of normal 42 in this study)/ A repeat test the following day was 61 U/L and at the end of the study 56 U/L. Neither of these abnormalities was reported as an adverse event.

Overlapping with these abnormal laboratory results was an adverse event of "common cold" beginning two days prior to the pre-dose Period 5 visit and continuing for 3 days after the visit.

Given the proximity to the adverse event "common cold" it is likely the increased CK was related to this illness.

Protocol: R076477-P01-1010; Subject: 101017

Subject 101017 was a white 27-year old male randomized to receive ER OROS paliperidone 12 mg during Period 1, ER OROS paliperidone 9 mg during Period 2, ER OROS paliperidone 15 mg during Period 3, ER OROS paliperidone 6 mg during Period 4 and ER OROS paliperidone 3 mg during Period 5. This subject completed all 5 periods of the study. The washout in between trial medication administration was at least 9 days.

Cmax levels were 18.2 ng/mL in period 1, 11.1 ng/mL during period 2, 20.1 ng/mL during period 3, 6.38 ng/mL during period 4 and 2.23 ng/mL during period 5.

The laboratory results from the sample obtained at the pre-dose Period 4 visit demonstrated a CK of 3394 U/L (upper limit of normal 545 U/L in this study) compared to a value of 240 U/L during screening. At the pre-dose Period 5 and end of study visits the levels were within the normal range (135 and 132 U/L respectively). Also at the per-dose 4 visit the ALT and AST were elevated (54 U/L and 90 U/L respectively) compared to values during screening of 27 and 32 U/L respectively. At the pre-dose Period 5 visit both had normalized with ALT 34 U/L and AST 35 U/L (upper limit of normal 53 and 42 U/L respectively). None of these abnormalities was reported as an adverse event.

No other adverse events were reported around the time of these abnormalities, but a comment in the Case Report Form said the "subject had been stressing his muscles thus CK was elevated predose"

Protocol: R076477-P01-1010; Subject: 101038

Subject 101038 was an asian 22 year-old male randomized to receive ER OROS paliperidone 15 mg during Period 1, ER OROS paliperidone 12 mg during Period 2, ER OROS paliperidone 3 mg during Period 3, ER OROS paliperidone 9 mg during Period 4 and ER OROS paliperidone 6 mg during Period 5. This subject completed all 5 periods of the study. The washout in between trial medication administration was at least 9 days.

Cmax levels were 34.6 ng/mL in period 1, 16.1 ng/mL during period 2, 7.58 ng/mL during period 3, 14.2 ng/mL during period 4 and 11.3 ng/mL during period 5.

The laboratory results from the sample obtained at the pre-dose Period 2 visit demonstrated a CK of 3173 U/L (upper limit of normal 545 in this study) compared to a value of 140 U/L during screening. At the pre-dose Period 3 visit this had normalized to 470 U/L. Also at pre-dose Period 2 the AST was elevated at 50 U/L (upper limit of normal 42 U/L) and LDH at 300 U/L (upper limit of normal 227 U/L). At the pre-dose Period 3 visit both AST and LDH had normalized (33 U/L and 156 U/L respectively).

At the time of the initial abnormalities the adverse events of mild doubtfully related "chest pain (muscular)", mild doubtfully related "elevated AST", mild doubtfully related "elevated creatine kinase" and mild doubtfully related "elevated LDH" were reported.

Given the timing of the adverse event muscular chest pain, the elevated CK value was likely related to this event.

Attachment 3 Recommendations for a Cardiorenal Consult Request (3 pages)
Recommendations for questions for the consultant and of information to be provided for the consultant were e-mailed to Dr. Ni Khin on 8/7/06 (upon her 8/7/06 e-mailed request) and are copied below. OCPB input on questions and on information to provide for the consultant was also recommended with respect to PK and PK-pharmacodynamic relationships (specifically regarding effects on the cardiovascular system).

1) is there sufficient information to recommend a maximum dose-level for adequacy safety based on hemodynamic and QT effects and for higher risk populations, while taking into account potential PK-PD interactions and PK effects (such as the food effect)?
2) If so, then please recommend a maximum dose-level, starting dose-level and recommended titration of the dose in healthy patients and in special populations with respect to adequate cardiovascular system safety (while noting that from an efficacy standpoint a 6 mg starting dose is probably best, while the some subjects may respond to the 3 mg daily dose-level).
3) Please recommend any key cardiovascular system findings that they think we should consider for description under Warnings/Precautions and any additional comments relevant to safety with respect to key findings (see Section 9 of the Clinical review).

I recommend (as in the above) that cardiorenal not only assess QT effects but also vital sign effects, not only because they could be inter-related or vital sign effects could influence QT results, but also because of the following. The overall hemodynamic effects of the drug (which could or could not be related to QT effects) are likely to lead to further clinically remarkable complications such as ischemia or other effects (e.g. consider drug effects on cardiac output) that were sometimes observed in ADOs or SAEs of young subjects that appeared to be healthy or could exacerbate pre-existing conditions as discussed in my review is the above sections).

Given the above Qs I have drafted recommended comments for the consult form, as requested (italicized text below).

Paliperidone NDA proposes treatment of this drug for schizophrenia at doses ranging from 3-12 mg. QT prolongation, other ECG and vital effects were observed in Phase III trials (used up to 15 mg/day), and in longterm open-label (OL) trials (using 3-12 mg daily flexible dose) with results suggestive of greater effects after approximately 6-12 months of OL treatment. Paliperidone (Pal) is a major active metabolite of risperidone (of which risperidone is also active, as described in Risperdal labeling). Yet, QT prolongation effects were not observed in Risperidone trials and vital sign effects described in labeling were quite limited with risperidone (as described in labeling for Risperdal). Risperdal is an immediate release formulation while [redacted] Pal is a longer acting (OROS) formulation. Pal also shows food effects (in contrast to Risperdal which is not described in labeling as showing food effects). ECG and vital sign effects of Pal vary over time as described in the clinical review (in some cases could be reflecting a PK-PD interaction effect or a Pal-interaction effect with underlying physiological-cardiovascular changes related to potential confounding variables or other factors). Also consider potential dynamic effects of Pal induced vital and ECG changes (e.g. under conditions of challenging the cardiovascular system in addition to potential static or absolute effect drug effects). The potential PK-QT relationship was further explored in an ECG study described in the NDA (Study -SCH-1009) which used an immediate-release Pal formulation in order to achieve up to "supra-therapeutic" plasma levels. However, note that this study had an uptitration phase (as subjects were monitored) and that QT prolongation effects appeared to "recur" or become greater upon an increase in dose-level and after

multiple dosing at a given dose level (they examined QT after 4 days on the highest daily dose level of 8 mg daily after a titration phase using a starting dose of 4 mg). More recent results (provided in response to an inquiry about this study), showed the following. Pal group mean QTc (QTcF and QTcLD) increases (from the averaged baseline values) of approximately 10-12 msec at that was generally near 1 1/2 hours post-dose on the ECG assessment day when treatment was initiated (4 mg) and on subsequent test days when the daily dose-level was increased or after multiple daily dosing at a fixed dose-level (only the highest 8 mg daily dose-level was examined for a MD effect at a given fixed dose-level). Gender differences may also exist. Study SCH-1009 did not examine vital sign drug effects and consequently the PK-vital sign drug effect relationship was not examined, as well. Food effect studies (section 7.1.12 of the clinical review) included multiple post-dose vital sign assessments and showed possible drug-effects (e.g. between fed versus fasted conditions but a placebo group was not included). Phase III trials also included fewer, yet multiple post-dose time-points showing effects a specific time-points (as described in Section 7.1.8 of the clinical review). ECG effects were also observed a certain time-points (as described in ECG related sections of the clinical review). Also note observations in the elderly Phase III trial (Study -302 that included a potential signal for AV block AEs and blood pressure changes, and other findings). Also note remarkable subjects in Section 7.1.3.3 of the clinical review, including a subject with syncope and sinus pause (nature of the syncope, etc is unclear) and other remarkable subjects.

Please contact Dr. Karen Brugge and (Ron can insert his name if he wishes) for any questions on the above or questions with locating key information.

Additional New QT prolongation Results:
Refer to a response e-mail to our inquiry about Study -1009 (3 e-mails sent on 6/29/06 from one of the sponsor's personnel Beth Getere-Douglass attached below). Note that these responses are similar to tables 109 and 108 provided in the clinical review of Section 7.1.12 A of the clinical review of the NDA) and provide similar results by gender, as requested. See the clinical review for additional information (as listed below). Also see figures of individual subjects (of QTcLD and plasma levels over time) in Appendix 4.3 of the original NDA (in the CSR for Study -1009) which shows peak QTcLD intervals in some subjects occurring near Cmax or after Cmax is achieved (this could be reflecting a delayed effect of Cmax). Also some subjects showed an additional rise in QTcLD values a number of hours (e.g. 12 hours post-dose in Subject 109088 on page 315 in Attachment 4.3 of the CSR) after Cmax is achieved (very few assessment time-points were conducted after the initial 4 hour-post-dose time-period such that it is not clear how high QTcLD would have reached in a given subject).



FW: Outstanding SCH-1009 Qs &..
FW: Outstanding SCH-1009 Qs &..
RE: Outstanding SCH-1009 Qs &..

Other recommended sections of the clinical review and other sources: :
It is suggested that the consultant start with reading the following sections of the Clinical review: Sections I and 9, Section 7 (the overview section that starts on page 70), Section 7.1.3.3 (and also section 7.1.1, 7.1.2, 7.1.3 for summary tables of deaths, ADOs and SAEs), Section 7.1.4, 7.1.8 (vital sign results) and 7.1.9 (ECG results). Sections 7.2.9 (includes more longterm exposure info on QT and related observations in a 120-Day SUR), section 7.1.12 which focuses on the ECG study (-SCH-1009) and food effect studies with vital sign info (that had no meaningful ECG results as I recall due to ECGs only occurring at baseline and sometimes a end-of-study assessment days post-dose). These sections also provide tables and figures with results. Section 5 of the clinical review also shows some PK results, as

provided by the sponsor that may be useful (but also refer to information provided by the OCPB reviewer, Dr. Ronald Kavanagh).

Also refer to olanzapine labeling (which has hemodynamic and related sections under Warnings/Precautions including findings of bradycardia and sinus pause and other findings). Also refer to Risperdal labeling which does not describe cardiovascular system findings observed with paliperidone despite that paliperidone is the major active metabolite of risperidone (while noting that risperidone is also an active compound).

Attachment 4 Sponsor's Response to a Request for More Information on Subjects 300541 and 100963

Subject 300541 (SCH-304) was a 50-year-old white male with a medical history of asthma, intermittent headaches, agitation, and insomnia. The physical examination at screening was normal. There was no relevant history of bradycardia, hypotension, dizziness, or syncope. His weight was 131.5 kg (body mass index 39.3 kg/m2).

At baseline, the ECG was reported as abnormal but not clinically important, showing left anterior fascicular block and a heart rate of 61 beats per minute (bpm). Blood pressure at baseline was 114/84 mmHg (standing) and 112/82 mmHg (supine); his pulse rate was 82 bpm (standing) and 82 bpm (supine).

On Day 5, while receiving paliperidone 12 mg/day, the subject was reportedly hypotensive, dizzy and fainted. The serious adverse events of *dizziness* (dizziness-verbatim) and *hypotension* (hypotension-verbatim) and non-serious adverse events of *syncope* (syncope-verbatim) and *psychotic disorder* (exacerbation of psychosis-verbatim) were reported on Day 5. The case record form does not contain further description of the actual syncope and no vital signs information or other descriptive information is available for Day 5. Study medication was stopped on Day 5 reportedly as a result of the exacerbation of psychosis ("requiring too much lorazepam": CIOMS). Lorazepam (1-7 mg/day) had been used during screening and throughout the first 4 days of double-blind treatment.

On Day 6 the subject was withdrawn from the study due to the adverse event "exacerbation of psychosis" and treatment with lithium 300 mg twice daily was initiated and on Day 7 aripiprazole 15 mg b.i.d. was added.

On Day 6 the subject was hospitalized and diagnosed with bradycardia (this term reportedly included the diagnosis of "pulse delay", both terms were reported as serious adverse events). His standing pulse rate of 38 bpm (40 bpm supine); his supine and standing blood pressures were 110/72 mmHg and 112/72 mmHg, respectively. A computed tomography scan revealed no acute intracranial process and no bleed, a chest x-ray was unremarkable, a basic metabolic profile, cardiac enzymes, T4 and thyroid stimulating hormone were all within normal limits. An ECG revealed normal sinus rhythm, left anterior fascicular block (present at baseline), possible lateral infarct of undetermined age, ventricular rate 67 bpm, PR interval 168 ms, QRS duration 100 ms and QT/QTc 408/431 ms (correction method not reported). A holter monitor reportedly demonstrated "several pauses including an 8-second pause". No further information was reported as the subject signed out/eloped from the hospital.

The dizziness, hypotension and syncope resolved in 2 days, the exacerbation of psychosis resolved in 13 days, and the bradycardia and delay in pulse resolved in 4 days.

The investigator assessed the serious adverse events "dizziness" and "hypotension" to be moderate in severity and possibly related to the study medication. The "exacerbation of psychosis" was rated mild and not related to study medication, the "syncope" mild and possibly related, while the serious adverse events "bradycardia" and "delay in pulse" were considered severe and possibly related to the study medication.

The subject had no prior symptoms of bradycardia, dizziness, or syncope, though there were ECG abnormalities at baseline. Dizziness, hypotension and psychosis have been reported with the use of paliperidone, although these events could also be due to the subject's underlying condition including anterior fascicular block, a potential signal of underlying cardiac disorders. This subject received 5 doses of 12 mg paliperidone; no re-challenge was performed. Therefore a causal relationship between the adverse events "syncope" and "exacerbation of psychosis" and the serious adverse events "dizziness" and "hypotension" and the intake of paliperidone is difficult to assess, but not possible to exclude. The lorazepam received throughout screening and the first four days of double-blind may also have played a role in the symptoms.

NOTE The following description is included because this subject's reason for discontinuation differed from the process described later in the document:
The subject was discontinued due to the adverse event of "exacerbation of psychosis", described as not related by the investigator. During the investigator meeting investigators were trained about what to do in the event a subject had an exacerbation of symptoms associated with their underlying schizophrenia diagnosis. They were instructed to differentiate between symptoms caused by the disease and those potentially caused by the drug. If in their clinical judgment the symptoms were caused by the disease (e.g. were consistent with past exacerbations) and were thus a result of the drug not working (e.g. lack of efficacy), they were to indicate the reason for withdrawal as "lack of efficacy". If their clinical judgment was that the drug was causing the symptoms, they were instructed to list the reason for withdrawal as the adverse event of exacerbation. While these instructions would have suggested this subject should have been discontinued due to "lack of efficacy", it is ultimately up to the investigator to select the reason for discontinuation.

b) Subject 100963: Please provide more complete information on this subject (include relevant information that may help to determine the etiology). Please also provide a hospital report (e.g. discharge summary) on this subject who died in transit to another hospital and any autopsy report (if one was performed). We are also wondering why this subject was prescribed trihexyphenidyl (e.g. "as needed" for what)?

Subject 100963 (SCH-301/701) was a 23-year old female non-smoker, who received primarily paliperidone ER 12 mg and had completed approximately 12 of the 14 weeks of run-in/stabilization in the recurrence prevention study at the time the study was stopped early on the basis of positive efficacy at the interim analysis. The subject was enrolled in the open-label extension and treated with paliperidone ER 12 mg and trihexyphenidyl for EPS treatment and prophylaxis. At the last recorded open-label extension visit (Week 16 in the open-label extension), the subject was experiencing no new symptoms, had no delusions or hallucinations and sleep and appetite were reportedly normal. PANSS total score was 40, CGI-S was 3 ("mild") and AIMS/BARS/SAS scores were all 0. Her score on the Personal and Social Performance (PSP) scale was an 80 (100 indicating the highest functioning). Blood pressure on that date was 116/80 mmHg supine, 112/80 mmHg standing, and heart rate was 80 bpm supine and 84 bpm standing. ECG showed a heart rate of 81 bpm, QRS axis was 78, rhythm was normal sinus rhythm, and repolarization pattern was normal. The subject failed to show up for her next appointment after she had been treated without tolerability issues for approximately 28 weeks and the investigative site made multiple attempts to contact her.

Approximately 5 weeks later, the site was able to obtain information from a relative and learned the subject had died around the time of the missed appointment. Initially, the family refused to provide further information to the site. Subsequently, the site obtained the following information. On the day of her death, the subject's mother described her as anxious, agitated and complaining of breathlessness. The mother gave her a dose of trihexyphenidyl 2 mg (prescribed for EPS). The subject later reportedly vomited, shortly thereafter experienced "severe convulsive movements of the entire body" and became unconscious. She was taken initially to a nearby practitioner who directed them to a hospital where she was examined and found to be unresponsive to painful stimuli and had only deep tendon reflexes present. She was maintained in the hospital for 3 hours on IV fluids and demonstrated a gradual fall in her blood pressure. She received oxygen and phenytoin. She experienced no further convulsions. Laboratory results showed a random plasma glucose of 102 mg/dL, sodium 126 mmol/L, potassium 3.1 mmol/L and chloride 99 mmol/L. Neither an ECG nor an EEG was performed. A decision was made for her to be transferred to a second "better equipped center". She reportedly died on route to the second facility. No autopsy was performed and as the subject lived in a very rural region of India, there is reportedly no death registry, thus no death certificate is available. Also there is no hospital record or discharge summary available.

The treating physician did not believe there were signs of drug use, overdose or poisoning of any kind, but no specific tests were obtained. Her clinical diagnosis was postictal stupor/postictal coma, with bronchospasm and pulmonary thrombo-embolism considered in the differential diagnosis.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Brugge
8/18/2006 04:26:23 PM
MEDICAL OFFICER

Ni Aye Khin
8/31/2006 03:11:07 PM
MEDICAL OFFICER
See memo to file for additional comments.

CLINICAL REVIEW

Application Type	NDA 21-999
Submission Number Code	N000
Letter Date	11/30/05
Stamp Date	11/30/05
PDUFA Goal Date	9/30/06
Reviewer Name	Karen Brugge, MD
Review Completion Date	7/21/06
Established Name	Paliperidone
(Proposed) Trade Name	[redacted]
Therapeutic Class	Atypical Antipsychotic
Applicant	Johnson & Johnson
Priority Designation	Standard
Formulation	Extended Release OROS® oral tablets
Proposed Dosing Regimen	6 mg administered daily in the morning, may benefit from lower or higher doses within the recommended daily dose range of 3 mg to 12 mg once, daily.
Indication	Schizophrenia
Intended Population	Adults with Schizophrenia

1 EXECUTIVE SUMMARY

The Purpose of This Review.

[redacted] The summary provides a brief overview of the Clinical review of this NDA (refer to the review for more complete and detailed clinical information and clinical recommendations).

Recommendations in this review are being provided from a clinical perspective. Reviews from other disciplines are pending at the time of this writing.

Proposed Indication and Treatment
The proposed indication is Schizophrenia in the acute episode (in adults).

The sponsor proposes a daily oral dose of 6 mg of OROS Paliperidone (Pal) to be taken in the morning. Proposed labeling also specifies that patients may benefit from lower or higher doses within a recommended daily dose range of 3 to 12 mg (once daily).

1.1 Recommendation on Regulatory Action

An approvable action is recommended from a clinical perspective.

All comments and recommendations below are provided from a clinical perspective (in the opinion of the undersigned reviewer).

Pivotal Phase III trials were positive for establishing adequate efficacy, pending confirmation by the Office of Biometrics. The recommended dose in proposed labeling is also reasonable from an efficacy standpoint. However, there are several key issues that primarily pertain to establishing an adequately safe, yet efficacious dose range of Pal. Extensive experience with the already marketed Risperdol® provides some support in favor of the adequate safety of Pal. Yet, some key issues specific to Pal need to be resolved, such as a food effect on plasma levels, QT prolongation effects observed in Phase III trials and in a QT Prolongation study, among other safety findings that were not revealed in the Phase III trials of risperidone that supported approval for Risperdal® (as described in labeling). Input from the Office of Clinical Pharmacology and Biopharmacy (OCPB) is critical in determining an adequately safe dose and treatment regimen, as outline below. OCPB input is recommended for other issues, as outlined below. Ultimately the risk: benefit ratio relative to the already available risperidone needs to be addressed. An Advisory Committee will be held in September of 2006.

If an approvable action is granted at the Agency level on this NDA, then recommendations are provided below starting with a recommendations that impact on both safety and efficacy,

followed by safety specific recommendations and efficacy-related recommendations follow, thereafter.

Recommendations that impact on both safety and efficacy:

1. The recommended starting dose and dose-range appears to be reasonable from an efficacy perspective but there are safety issues that also impact on dose, as described below. Therefore, these safety issues need to be addressed, as well before a recommended dose range can be made.
2. It is not clear if the to-be-marketed formulation was used in all pivotal efficacy trials (this question was conveyed to the sponsor and a response is pending at the time of this writing). OCPB input may be needed if a different formulation was used.

Safety Related Recommendations

If an approvable action is granted at the Agency level on this NDA, then the following outline contains comments and recommendations regarding safety (refer to Sections 7 and 9 of this review for an outline of safety findings, including those that are the basis of issues below):

1. A food effect on the pharmacokinetic (PK) properties of Pal was observed in two Phase I trials, as described in Section 5 of this review. This issue needs to be resolved with respect to recommendations for an adequately safe, yet efficacious treatment regimen. OCPB input is critical and recommended.
2. Food effects on PK and safety (in Phase I food effect studies described in Sections 5 for PK effects, 7.1.12 C and Section 7.1.3.3 for safety findings)
3. Several cardiovascular-related findings need to be addressed from a dose-level perspective that include a signal for
    a. QT prolongation (based on Phase III data, updated longterm OL extension trial data provided in the 120-Day SUR, results of Study –SCH-1009),
    b. Results on heart rate (based on ECG and vital sign results), and other hemodynamic effects were observed (based on results in Section 7). Subjects with clinically remarkable events related to hemodynamic Pal effects are also described in Section 7.1.3.3 of this review.
    c. Potential PR interval prolongation effects as suggested by the following observations:
        i. A greater incidence of adverse events (AEs) of ° AV block in the 15 mg (highest-dose) Pal group compared to placebo (4.4%, 1.4%, respectively)
        ii. Similar findings in the small elderly Phase III trial (3% and 0% in the Pal and placebo groups, respectively) that used a flexible dose design (3-12 mg/day),
        iii. A small group mean increase in PR interval in Pal compared to placebo groups in Phase III trials (the magnitude of this increase was clinically unremarkable)
4. [redacted]

5. OCPB input is recommended regarding dosing recommendations in light of QT prolongation and other adverse effects and the potential PK-pharmacodynamic (PD) interactions (as well as other factors impacting PK such as a food effect, drug-drug interactions and others). Effects on QT and vital sign appear to be influenced by Cmax and Tmax (e.g. not only absolute levels but also perhaps how quickly levels are rising) and by other confounding variables (due to observations of direct or indirect time-dependent effects observed in Phase III trials and in Study –SCH-1009).
6. A more gradual dose adjustment (with a lower starting dose and longer interval between dose increments) and a lower maximum dose-level (not-to-exceed level) should be recommended for elderly patients and any other special populations, pending input from OCPB. It is noted that Risperdal® labeling provides specifications on dose adjustment in this section of labeling, although the recommendation is not specific to a given dose-level or maximum dose-level. This recommendation is being made on the basis of the following:
    a. Safety findings in the elderly trial (-302), as outline in Sections1.1, 7 and 9 of this review,
    b. Multiple concomitant medications and diseases are common in the elderly
    c. The elderly are generally considered to have greater vulnerability to adverse effects (e.g. cardiovascular, ECG, CNS and other effects)
    d. The elderly are more predisposed to alterations in PK (towards greater plasma levels),
    e. There is the additional concern of a food effect on PK
    f. A safety signal was revealed for increased risk of mortality in elderly patients with dementia being treated with atypical antipsychotics in longterm clinical drug trials (as described in drug class labeling of approved atypical antipsychotic agents). The role of age in this signal remains unclear.
7. Elevations in CPK levels were observed in treatment groups in Phase III trials. However, these elevations were inconsistent across treatment groups and may be reflective of the patient population rather than being drug-related. Yet, CPK levels varied widely across subjects and showed large fluctuations over time within a given subject. Furthermore, baseline levels were elevated in some subjects and in some treatment groups. Consequently, it is difficult to detect a potential drug signal in a population with highly variable CPK levels at baseline. CPK elevations were also observed in Phase I trials of generally healthy subjects (who did not have schizophrenia) that appeared to be dose-dependent in subjects treated with the OROS formulation.

    The sponsor does not describe any serious events associated with CPK elevations except for one subject (and possibly another with NMS that was found by the undersigned review; subjects 100057 and 200213). Additional subjects with elevated CPK were however, found by the undersigned reviewer that also had elevations in LFTs (as described in Section 7.1.3.3 of this review). There may be additional subjects with

clinically remarkable events associated with CPK elevations since results of a special data analyses for revealing a potential drug-related signal could not be found in the Summary of Clinical Safety (SCS) section of the submission which provided the integrated summary of safety in clinical drug trials. Therefore, it is not clear to the undersigned if CPK elevations were associated with dystonia or other drug-related adverse effects. Another consideration is that CPK elevations reflective of the patient population would be expected to occur primarily in the acutely psychotic patient, yet elevations were also revealed during longterm OL Pal treatment (in the Phase III OL extension trials). This potential safety signal should be adequately resolved.

8. It is recommended that the specific methodology for dose adjustments during the OL trials (-702, -703, -704, and -705) be clarified (these trials used a flexible dose design). This information is relevant to longterm safety and may influence recommendations for dosage and administration in labeling.
9. Attachment 1 of this review lists questions raised to the sponsor to which some responses were received and other responses are pending at the time of this writing that should be resolved before considering a final approval action on this NDA (since some responses arrived late in the review cycle a review of these responses is pending, unless otherwise specified in this review).
10. Section 7.2.8 (on quality and completeness of data) discusses concerns related to identifying potentially clinically remarkable subjects with a specific type of AE (e.g. syncope, suicidality, among others). These issues should be adequately resolved. See Attachment 1 that includes some questions related to this concern (as described in the pervious item).
11. Once efficacy and safety related issues can be adequately addressed, then the sponsor would need to provide a convincing justification that the benefit: risk ratio of Pal outweighs that of Risperdol® (Ris).
12. Input from other disciplines is pending at the time of this writing.

Section 9 of this review provides key recommendations for labeling if an approvable action is granted at the Agency level on this NDA.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The proposed Risk Management program cannot be found in the submission. In accordance with the Clinical Reviewer MAPP, a postmarketing studies and surveillance plan should be described here. Sponsors generally conduct ongoing postmarketing surveillance for safety signals and maintain a database. Sponsors of approved NDAs are also required to submit Periodic Safety Update reports according to regulations. Input from the Office of Surveillance and Epidemiology is a consideration, as well, if the Agency grants an Approvable Action.

1.2.2 Required Phase 4 Commitments

It is recommended that the sponsor address key issues, as discussed in this review (and as outlined above) before considering Phase 4 commitments.

The following are some considerations for studies that should enhance our understanding of cardiovascular effects of Pal:

- Conduct cardiovascular challenge tests (at baseline and during treatment) in double-blind, placebo controlled studies of patients with schizophrenia while monitoring vital signs and ECG (and in some cases with telemetry monitoring) using the following challenge paradigms for each given study:
  - Challenge subjects with a commonly used drug in the population that is known to have some degree of QT prolongation effects using adequately safe doses that would allow for detecting a signal while assuring adequate safety (e.g. the undersigned reviewer is the primary reviewer on the escitalopram NDA 21323 in which a pimozide-escitalopram interaction study revealed greater QT effects with this combination than with either of the two drugs alone.
  - Challenge subjects with a tread mill stress test (using methods for an adequately safe study).
  - Challenge subjects with a tilt table test
- Challenge subjects on longterm OL Pal (over 6 months to up to a year of treatment) with a higher daily dose of Pal (that is adequately safe) to determine if vital sign and QT effects can be elicited after a single dose and after subsequent multiple daily doses until at least steady state levels are achieved (subjects should undergo monitoring prior to starting the OL Pal treatment and throughout OL treatment to allow for pre-challenge and pre-Pal comparisons on cardiovascular parameters).
- Conduct a food challenge (food effect) study in patients with schizophrenia to examine the role of food effects on safety parameters (input from OCPB is recommended on this recommendation).
- Conduct studies to better characterize drug-drug and drug-disease interactions on cardiovascular effects and other relevant safety parameters.
- Other safety issues and PK issues may require further examination depending on the sponsor's responses to issues and on OCPB input.

There is the belief that antipsychotic drug treatment may be associated with or induce a metabolic syndrome (e.g. weight gain, abnormal lipid profile, hyperglycemia and other changes) that may increase risk for morbidity and possibly mortality in this population. Also consider a role of potential alterations in the endocrine system that may yet to be revealed or are known to exist (e.g. increased prolactin levels). Therefore, further study in this area should be considered.

Since elevations in LFTs were observed in some Pal subjects further study in this area should be considered such as employing a challenge test to determine if elevations can be elicited using methods that would be adequately safe. For example consider a study examine the effects of coadminstration of olanzapine (refer to labeling describing LFT elevations in some subjects on

this drug). Polypharmacy involving multiple antipsychotic medications is not uncommon among clinicians treating patients with schizophrenia.

Phase III clinical trials using the OROS® formulation did not appear to test stools for bleeding and to monitor for excretion of capsules. A small group mean decrease in HgB was also observed that in itself is not clinically remarkable, yet could be reflecting a real drug-related effect (e.g. gastrointestinal bleeding perhaps due to retention of capsules). There was one subject with duodenal rupture and another subject with gastrointestinal hemorrhage reported in Phase III trials. It is recommended that consideration be given to studies focusing on a potential effect on OROS versus an effect of Pal on HgB and gastrointestinal bleeding, while also closely monitoring for signs and symptoms for GI complications, monitoring stools for occult blood and retention of capsules which were not systematically evaluated in Phase III trials.

1.2.3 Other Phase 4 Requests

See the previous section in which key issues first need to be addressed that can impact on the nature of Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Paliperidone (an extended release oral OROS® formulation) is in the drug class of atypical neuroleptic agents and is a major active metabolite of risperidone. Risperidone is approved for treatment of Schizophrenia. Paliperidone and risperidone are atypical antipsychotic agents and are in the chemical class of benzisoxazole derivatives.

Three pivotal multicenter, placebo controlled, active controlled, randomized, double-blind (DB), fixed dose-response, parallel group trials were conducted to establish efficacy of oral paliperidone administration for the treatment of Schizophrenia (Studies R076477-SCH-303, R076477-SCH-304, R076477-SCH-305). The daily oral doses among these trials ranged from as high as 15 mg daily (in Study R076477-SCH-305) and as low as 3 mg in Study R076477-SCH-303. The 15 mg treatment group was started on 12 mg daily for the first seven days of treatment following by 15 mg daily for the remainder of the DB phase. The active control groups in these trials received olanzapine (10 mg daily). Two studies included subjects from the United States while the third study was conducted in eastern and western European countries, as specified in the submission.

A total of 1665 subjects were in the intent-to-treat (ITT) population (defined as a randomized subject with at least one dose of study drug and at least one post-baseline efficacy assessment) of which 351 subjects received placebo, 955 subjects received paliperidone (extended release OROS® formulation) and 359 subjects received active control drug (10 mg daily of olanzapine). Subjects were 18 to 65 year old (a few subjects over 65 years old) generally healthy men and women with Schizophrenia for at least one year using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Subjects were required to have a Positive

and negative Symptom Scale total score of 70 to 120 at baseline and were inpatients for at least 14 days during the study.

An additional Phase III trial (R076477-SCH-302) was conducted on elderly patients using a flexible dose design (3-12 mg daily of paliperidone. Other aspects of the study design of this trial were generally similar to that employed in three above described pivotal trials of non-elderly adults. The ITT population consisted of 114 total subjects of which 76 subjects received paliperidone and 38 subjects received placebo.

Safety was assessed in the 3 pivotal trials, as well as in additional Phase I, II and III trials. Section 7 of this review provides more details on safety.

1.3.2 Efficacy

Pivotal Trials

Each pivotal Phase III trial (Studies R076477-SCH-303, R076477-SCH-304, R076477-SCH-305) was positive for efficacy. Refer to the previous section for a description of these studies and enumeration of subjects. The primary efficacy measure was the mean change from baseline to treatment endpoint on the Positive and negative Symptom Scale (PANSS) total score (a standard measure for Phase III trials for establishing efficacy in treating schizophrenia). Greater improvement was observed with paliperidone treatment compared to placebo treatment. Improvement was demonstrated for all dose levels examined (3, 6, 9, 12 and 15 mg daily doses administered in the morning).

Results on secondary variables in each of these short-term Phase III trials were also generally consistent with findings on the primary efficacy variable.

The elderly Study -302 showed at least trends for greater improvement. This study was small such that failure to show significant group differences may be due to insufficient sample size. Due to the small sample size in this study, the results are difficult to interpret.

Key Issues Relevant to Efficacy and Proposed Labeling
See Section 1.1 above. The last section of this review also addresses key issues.

1.3.3 Safety

See key safety issues under Section 1.1. Section 7 of the review provides a detailed discussion of safety findings.

In addition to pivotal DB Phase III trials and a small DB Phase III elderly trial, the safety results were also provided for ongoing longterm open-label trials that were extension trials to the short-term (6-week) DB Phase III trials. The results of the OL trials provided longterm safety results for 6 and 12 month exposures within ICH guidelines within the dose-range being recommended for treatment in proposed labeling.

Study –SCH-1009 provided results on QT prolongation effects of a non-OROR (more immediate release) formulation of Pal. This review also describes results of a few other Phase I trials that provided some safety results in fed and fasted treatment conditions, as the effect of food on PK was examined and conducted more frequent vital sign assessments, than was employed in the Phase III trials.

Section 7 describes safety findings.

1.3.4 Dosing Regimen and Administration

The sponsor proposes a daily oral dose of 6 mg to be taken in the morning. Proposed labeling also specifies that patients may benefit from lower or higher doses within a recommended daily dose range of 3 to 12 mg (once daily).

See Section 1.1 for comments relevant to dosing and administration with respect to key safety issues and food effects.

1.3.5 Drug-Drug Interactions

Drug-drug interactions were not systematically evaluated in Phase III trials. See section 1.1 for comments and recommendations on potential drug-drug interactions relevant to key safety related issues.

1.3.6 Special Populations

See Section 1.1 for comments and recommendations relevant to the elderly population and relevant to key safety findings in a small Phase III trial on elderly patients. This topic is covered in various sections of this review.

2 INTRODUCTION AND BACKGROUND

Note to the Reader: A reviewer MAPP was followed for this review which involves having multiple headings with redundancy across sections. An effort has been made by the undersigned reviewer to minimize this redundancy without jeopardizing the flow of the content. Figures and tables provided in this review were generally obtained from the NDA submission.

The Purpose of this Clinical Review (copied from Section 1). The purpose of this clinical review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-999. The information in this review and recommendations are provided from a clinical perspective.

Proposed Indication (also in Section 1). The sponsor is seeking approval of Paliperidone OROS® oral formulation (Pal) for the treatment of schizophrenia in adult patients.

A Brief Overview of the Organization of this Review. The undersigned reviewer has attempted to follow the required Clinical Reviewer Template MAPP which was finalized approximately one year ago. Since the organization of this review, as required by the MAPP is generally new to the regulatory reading audience the following provides some comments intended to aid the reader.

All sections, subsections (which are numbered) and the order and placement of these sections and subsections in this review are according to the required template. However, please note the following:

- Note that some subsections such as clinical microbiology (section 6.1.5) appear under efficacy but is not relevant to this review.
- In order to avoid redundancy between various subsections, related subsection(s) are referenced, rather than repeating the same information under multiple subsections.

Italicized text in this review appears in various places throughout this review and is intended to denote comments, conclusions and recommendations being made by the undersigned reviewer (from a clinical perspective), unless otherwise specified. Sometimes a result section has both reviewer comments/conclusions embedded with the sponsor's results. These sections generally present the results found in the submission (unless otherwise specified). Consequently, these sections that contain some of the sponsor's results along with reviewer comments are also italicized.

2.1 Product Information

The pharmacologically active compound in Pal is 6-OH Risperidone which is the major metabolite of risperidone (Ris). The OROS® formulation is considered as a slow release

formulation. Ris is marketed (as Risperdol®) as a tablet formulation which is a more immediate release formulation compared to Pal. Risperdol® is approved for the treatment schizophrenia.

2.2 Currently Available Treatment for Indications

Pal is in a drug class of atypical antipsychotic agents and several drugs in this drug class are approved for treatment of schizophrenia and other psychiatric indications. See the previous section regarding Ris which is one of these approved drugs and is metabolized primarily to 9-OH Ris which is the active compound in Pal.

2.3 Availability of Proposed Active Ingredient in the United States

See section 2.1 above describing Ris which is approved for treatment of schizophrenia and is metabolized primarily to 9-OH Ris which is the active compound in Pal. Pal is not approved for the market in the United States.

2.4 Important Issues With Pharmacologically Related Products

See the previous section and other safety related sections of this review, as well as current approved labeling for drugs in this drug class and the final section of this review.

2.5 Presubmission Regulatory Activity

Pal was developed under IND 65850. The sponsor has had several meetings with the Division (EOP II, Pre-NDA meetings) under IND 65850. The sponsor provides copies of meeting minutes in the submission.

2.6 Foreign Marketing Experience

Section 5.11 of Module 2.5 of the submission specifies that "ER OROS paliperidone has not been marketed in any country to date."

The sponsor does provide world-wide postmarketing safety information on risperidone which was first approved in 1992 in the United Kingdom and is also approved by the Agency for US marketing, as previously described.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC information is provided in the submission and is under review by the CMC Team at the time of this writing. The CMC reviewer, has no major CMC issues at the time of this writing or at the time of the mid-cycle review meeting.

3.2 Animal Pharmacology/Toxicology

The submission contains preclinical information which is under review by the Pharmacology Reviewer at the time of this writing.

3.3 Other Disciplines: Division of Scientific Investigations (DSI) and Biometric Disciplines

DSI is involved with this NDA and results are pending at the time of this writing.

The NDA is also under review by Biometrics at the time of this writing.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The following items were utilized during the course of this clinical review:

Documents Utilized in Clinical Review	
DATE	DESCRIPTION (electronic submissions unless indicated otherwise).
11/30/05	NDA 21-999 N000: the submission included Narratives hyperlinked to CRFs (were generally hyperlinked from the narrative or from tables listing narratives) for completed Phase I-III trials for serious adverse events (SAEs) and adverse dropouts (ADOs) using a cut-off date of 5/31/05. Safety (CIOMS) reports (of SAEs and ASDOs) were provided at the cut-off dates of 6/1/05-8/31/05 120-Day Safety Update Report Submission (N0002, letter date 3/29/06 and stamp date 3/29/06): Narratives of SAEs and ADOs were provided for the more recently completed Study -301 and for open-label trials (Studies -701-705) using the cur-off date of 11/1/05 (narratives or narrative summary tables generally included hyperlinks to the CRFs). Safety (CIOMS) reports were provided for SAEs and ADOs at the cut-off-dates of 11/2/05-12/31/05 This submission contained the bulk of longterm safety data from ongoing open label trials in which ICH guidelines for 6 and 12 month exposure was met. N0001 letter dated 1/10/06 response to pre-filing questions. <u>Additional Submissions with Clinical Information that were Received Late in the Review Cycle of which Some are in Response to Inquiries</u> The following submissions either have not been reviewed or not have been fully reviewed, since they were received late in the review cycle or contained only non-clinical information: • N007 6/27/06: responses to clinical inquiries • N006 6/15/06: 210-Safety Update Report and new Food Effect Phase I trial Results • N005 letter dated 6/15/06: responses to clinical inquiries • N004: letter dated 5/26/06: no clinical information could be found (CMC related) • N003: no clinical information could be found (CMC related) Not all information from these submission are described or were fully reviewed since some submissions were only submitted with 1-2 months of the internal reviewer deadline which is 7/22/06.

4.2 Tables of Clinical Studies

Tables in this section provide an overview of trials, study design and the number of subjects, as specified. More detailed information on the enumeration of subjects for efficacy and safety analyses is provided in Sections 6 and 7.2.1 of this review (in accordance with the Clinical Reviewer MAPP). In addition to information required by the Clinical Reviewer MAPP, Section 7.2.1 also provides the enumeration of subjects that completed key trials. Other subsections of 7.2 provide additional exposure information as required by the Clinical Reviewer MAPP.

Completed and Ongoing Phase III Trials
Phase III trials included:

- 3 pivotal Phase III trials of primarily non-elderly adult patients using a 6-week double-blind (DB) phase (Studies R06477-SCH-303, R06477-SCH-304, R06477-SCH-305). The sponsor specifies these 3 trials as providing results to support their proposed efficacy claim. These adult trials had very few elderly subjects.
- An elderly Phase III trial of patients using the 6-week DB phase (Study R06477-SCH-302). This trial was a small flexible dose trial that was otherwise almost identical in study design to the above 3 Phase III trials.
- Ongoing Phase III Trials include 1 ongoing Phase III trial on "prevention of recurrence" (Study R06477-SCH-301) and ongoing open-label (OL) extension phases of 6-12 months duration that are being conducted for longterm safety data. These longer term OL phases are extension phases (trials R06477-SCH-701, -702, -703, -704 and -705) that followed the 6-week double-blind phases of the 3 pivotal Phase III trials (Studies R06477-SCH-303, R06477-SCH-304, R06477-SCH-305), of one elderly Phase III trial (Study R06477-SCH-302) and of a Phase III trial on "Prevention of recurrence (Study R06477-SCH-301).

Since a food effect was observed in Phase I trials, it is important to note that dosing in the Phase III short-term trials (-302, -303, -304, -305) was to occur in the morning. The timing and content of meals (and the timing relative to dosing) were not monitored in the Phase III trials.

This review will generally be referring to trials by the last set of hyphenated digits of the trial number (e.g. -302 for Study R06477-SCH-302).

All tables below were provided in the submission with some additional information added by the undersigned reviewer for clarification purposes or to provide more detailed information (all of these additions are denoted by italics).

COMPLETED PHASE 3 DOUBLE-BLIND STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
Analysis Set Protocol No.	Study Design/Enrollment Statusa
Double-Blind Studies Analysis Set	
R076477-SCH-303 Western and Eastern Europe	A randomized, 6-week double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed dosages of paliperidone ER (6, 9, and 12 mg/day) and olanzapine (10 mg/day) in the treatment of subjects with schizophrenia. Double-blind: Completed No. Subjects Evaluable for Safety: 629 Treated with Paliperidone: 375
R076477-SCH-304 United States	A randomized, 6-week double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 2 fixed dosages of paliperidone ER (6 and 12 mg/day) and olanzapine (10 mg/day) in the treatment of subjects with schizophrenia. Double-blind: Completed No. Subjects Evaluable for Safety: 439 Treated with Paliperidone: 224
R076477-SCH-305 North America (includes the United States), Eastern Europe, Asia, Isreal, Mexico and South Africa	A randomized, 6-week double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed dosages of paliperidone ER (3, 9, and 15 mg/day)band olanzapine (10 mg/day) in the treatment of subjects with schizophrenia. *Reviewer Comment: the 15 mg group received 12 mg daily over the first week of DB treatment, followed by 15 mg daily thereafter during the DB phase.* Double-blind: Completed No. Subjects Evaluable for Safety: 614 Treated with Paliperidone: 364
Study R076477-SCH-302	
R076477-SCH-302 Easter Europe, South Africa and Greece	A randomized, 6-week double-blind, placebo-controlled study to evaluate the safety and tolerability of flexible doses of paliperidone ER in the treatment of geriatric subjects with schizophrenia. *Reviewer comment inserted here (based on information found on page 43-44 in the SCS): the flexible daily dose level used in this trial was 3 to 12 mg. Subjects were started on 6 mg daily over the first week and if tolerated, this dose daily dose was increased to 9 mg daily. Subjects that could not tolerate the 6 mg daily dose-level could have their dose decreased to 3 mg daily at any time during the first week. Dose increments could not occur more frequently that every 7 days, in increments of no greater than 3 mg daily. The lowest dose permitted was 3 mg daily.* Double-blind: Completed No. Subjects Evaluable for Safety: 114 Treated with Paliperidone: 76

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
a Enrollment as of 31 May 2005.
b Subjects in the 15 mg/day group received 12 mg/day on Days 1-7 and 15 mg/day for the rest of the double-blind phase.

ONGOING DOUBLE-BLIND PHASE 3 STUDY	
R076477-SCH-301	A randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension evaluating paliperidone ER in the prevention of recurrence in subjects with schizophrenia. *Reviewer comment inserted here: the trial involved an 8-week OL-run-in phase, then a 6-week OL stabilization phase, followed by a placebo controlled, DB treatment phase (1:1 of placebo or Paliperidone treatment). Treatment was flexible during the OL run-in and DB treatment phases (3 to 15 mg daily) but was fixed during the OL stabilization phase (at the dose identified during the stabilization phase).* Double-blind: Ongoing No. Subjects Enrolled as of 31 May 2005: 462 *Reviewer Comment inserted here: This study was completed in time for unblinded data to be provided in the 120-Day SUR.*

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005. [b]Subjects in the 15 mg/day group received 12 mg/day on Days 1-7 and 15 mg/day for the rest of the double-blind
se.

Ongoing Open-Label Extension Trials (Studies -702, -703, -704, -705)

The following table summarizes the ongoing extension phases (referred to as Studies -702, -703, -704, -705) to the completed 6-week double-blind pivotal (-303, -304, -305) and elderly Phase III (-302) trials. These studies used a flexible daily dose of 3 to 12 mg (dose levels of 3, 6, 9 or 12 mg/day), except Study -705 used a maximum allowable daily dose of 15 mg (3, 6, 9, 12 or 15 mg/day). Study –702 was conducted on elderly subjects, while the other OL studies were conducted on almost exclusively non-elderly adults.

Analysis Set Protocol No.	Study Design/Enrollment Status[a]
ONGOING OPEN-LABEL PHASE 3 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
Open-Label Studies Analysis Set	
R076477-SCH-702	A 26-week open-label extension to evaluate the safety and tolerability of flexible doses of ER OROS paliperidone in geriatric subjects with schizophrenia who completed the 6-week double-blind phase or discontinued due to lack of efficacy after a minimum of 21 days of double-blind treatment in Study R076477-SCH-302 *Starting dose was 9 mg and a flexible dose design was employed (3, 6, 9, or 12 mg/day) as described on page 45 of the SCS.* No. Subjects Enrolled as of 31 May 2005: 88 Ongoing
R076477-SCH-703	A 52-week open-label extension to evaluate ER OROS paliperidone in the treatment of subjects with schizophrenia who completed the 6-week double-blind phase or discontinued due to lack of efficacy after a minimum of 21 days of double-blind treatment in Study R076477-SCH-303 *Reviewer comment: Starting dose was 9 mg and a flexible dose design was employed (3, 6, 9, or 12 mg/day) as described on page 45 of the SCS.* No. Subjects Enrolled as of 31 May 2005: 473 Ongoing

R076477-SCH-704	A 52-week open-label extension to evaluate ER OROS paliperidone in the treatment of subjects with schizophrenia who completed the 6-week double-blind phase or discontinued due to lack of efficacy after a minimum of 21 days of double-blind treatment in Study R076477-SCH-304 *Reviewer comment: Starting dose was 9 mg and a flexible dose design was employed (3, 6, 9, or 12 mg/day) as described on page 45 of the SCS.* No. Subjects Enrolled as of 31 May 2005: 203 Ongoing
R076477-SCH-705	A 52-week open-label extension to evaluate ER OROS paliperidone in the treatment of subjects with schizophrenia who completed the 6-week double-blind phase or discontinued due to lack of efficacy after a minimum of 21 days of double-blind treatment in Study R076477-SCH-305 *Reviewer comment: Starting dose was 9 mg and a flexible dose design was employed (3, 6, 9, or 15 mg/day) as described on page 45 of the SCS.* No. Subjects Enrolled as of 31 May 2005: 403 Ongoing
Study R076477-SCH-701	
R076477-SCH-701	A 52-week open-label extension evaluating ER OROS paliperidone for the prevention of recurrence in subjects with schizophrenia who experienced a recurrence event or remained recurrence free during the double-blind phase of Study R076477-SCH-301 No. Subjects Enrolled as of 31 May 2005: ~36[b] Ongoing

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005. [b]Number based on unaudited enrollment information.

Phase I/II trials.

The next set of tables summarize Phase I/II trials categorized as trials conducted on healthy subjects, studies on patients with schizophrenia, and "Other Phase I studies."

Continued on the next page

Summary Tables of Each Set of Phase I/II Trials.

Protocol No. (Formulation)	Study Design/Enrollment Status[a]
	PHASE I/2a STUDIES IN HEALTHY ADULT SUBJECTS
R076477-P01-103 *Absorption, metabolism, elimination* (IR)	SD, OL in healthy males (CYP2D6 EMs and PMs) / oral dose, 1 mg ^{14}C PAL IR/ mass balance, metabolic pathways of paliperidone and excretion of PAL and its metabolites in urine and feces. No. Subjects Enrolled: 5 Treated with Paliperidone: 5
R076477-P01-1007 *Absolute bioavailability and enantiomer disposition* (IR and ER)	SD, OL, randomized, 5-way CO in healthy males and females (CYP2D6 EMs and PMs) / oral dose, 1 mg IR PAL, 1 mg PAL i.v., 3 mg PAL ER, 1 mg R078543 solution, 1 mg R078544 solution (fasting) / absolute BA of IR and PAL ER, enantiomer disposition and interconversion. No. Subjects Enrolled: 20 Treated with Paliperidone: 20
R076477-P01-1008 *Final bioequivalence and food effect* (ER)	SD, OL, randomized, 3-way CO in healthy males / single oral doses of 15 mg (9+3+3 mg) PAL ER, 15 mg PAL ER tablet (fed or fasting) / BE of Phase 3 formulation (9+3+3 mg) *vs.* highest strength (15 mg) of commercial formulation, food effect on highest strength commercial formulation. No. Subjects Enrolled: 80 Treated with Paliperidone: 80
R076477-P01-1010 *Dose proportionality* (ER)	SD, OL, randomized, 5-way CO in healthy males / oral dose, 3, 6, 9, 12 or 15 mg PAL ER tablet (fasting) / dose proportionality. No. Subjects Enrolled: 50 Treated with Paliperidone: 50
RIS-BEL-28 *PK in healthy subjects* (IR)	SD, DB, randomized, PC, 3-way CO in healthy males (CYP2D6 EMs and PMs) / oral dose, 1 mg IR RIS, 1 mg IR PAL, placebo / plasma and urine PK, relative BA, PD (prolactin). No. Subjects Enrolled: 9 Treated with Paliperidone: 9
R076477-BEL-1 *Relative bioavailability and food effect* (IR)	SD, OL, randomized, 3-way CO in healthy males and females / oral dose, 0.5 mg IR PAL tablet (fed or fasting), 0.5 mg IR PAL solution (fasting) / relative BA of tablet *vs.* oral solution, food effect on tablet. No. Subjects Enrolled: 12 Treated with Paliperidone: 12
ALZA C-2001-032 *Colonic absorption* (IR and Pilot ER)	SD, OL, randomized, 4-way CO in healthy males and females / oral dose, 3 mg osmotic module RIS, 3 mg RIS oral solution, 3 mg osmotic module PAL and 3 mg PAL oral solution / PK. No. Subjects Enrolled: 16 Treated with Paliperidone: 16
ALZA C-2001-039 *Dose zipping* (IR and Pilot ER)	MD, DB, randomized, PC, 4-way CO in healthy males and females / oral doses over 2 days of 5.5 mg PAL Ascend, 4.5 mg PAL Flat, 4 mg IR PAL, placebo / PK, evaluate PD (orthostatic hypotension and prolactin). No. Subjects Enrolled: 27 Treated with Paliperidone: 27
ALZA C-2001-019 *Dose zipping* (IR and Pilot ER)	MD, DB, randomized, PC, 5-way CO in healthy males and females / oral doses over 2 days of 6 mg RIS (RIS Ascend-6), 6 mg PAL (PAL Ascend-4), 4 mg PAL (PAL Ascend-2), 4 mg IR RIS (IR-2), placebo / PK, PD (orthostatic hypotension, prolactin). No. Subjects Enrolled: 30 Treated with Paliperidone: 30

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v. = intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a] Enrollment as of 31 May 2005.

Protocol No. (Formulation)	Study Design/Enrollment Status[a]
	PHASE 1/2a STUDIES IN HEALTHY ADULT SUBJECTS (continued)
ALZA C-2002-034 *Relative bioavailability and food effect* (IR and ER)	SD, OL, randomized, 4-way CO in healthy males and females / oral dose, 2x2 mg [redacted] OROS (fasting), 2x2 mg [redacted] OROS (= PAL ER, Phase 1 formulation) (fed or fasting), 2 mg IR PAL (fasting) / PK, BA of OROS formulations, food effect on PAL ER formulation, compare PD (orthostatic hypotension). No. Subjects Enrolled: 32 Treated with Paliperidone: 32
ALZA C-2003-044 *Pilot dose proportionality* (ER)	SD, OL, 4-period sequential in healthy males / oral dose, 6, 9, 12 and 15 mg PAL ER (3 and 9 mg tablets, Phase 3 formulation) / dose proportionality. No. Subjects Enrolled: 30 Treated with Paliperidone: 30
ALZA C-2004-006 *Tolerability* (ER)	SD, OL, randomized, sequential, parallel group in healthy males / oral dose, 12 mg and 15 mg PAL ER (fasting) (Group 1), or 15 mg PAL ER (fed or fasting) (Group 2), (3 and 9 mg tablets, Phase 3 formulation) / PK, dose proportionality, food effect, tolerability. No. Subjects Enrolled: 40 Treated with Paliperidone: 40
R076477-P01-101 *PK/PD* (Alternative ER formulations)	SD, OL, randomized, 5-way CO in healthy males and females / oral dose, 2 mg-eq. ER [redacted] PAL (2.5 mg [redacted] fed or fasting), 2 mg-eq. coated PAL ER (2x2 mg tablets, fed or fasting), 2 mg IR PAL (fasting) / PK of [redacted] food effect, compare PD (orthostatic hypotension). No. Subjects Enrolled: 35 Treated with Paliperidone: 35
R076477-P01-102 *PK/PD* (Alternative ER formulations)	SD, OL, randomized, 5-way CO in healthy males and females / oral dose, 2.5 mg [redacted] ER PAL [redacted] formulation 1 (fed or fasting), 2.5 mg [redacted] ER PAL [redacted] formulation 2 (fed or fasting), 2 mg IR PAL / relative BA o [redacted] formulations, food effect, compare PD (orthostatic hypotension). No. Subjects Enrolled: 35 Treated with Paliperidone: 35
R076477-SWE-1 *PET* (IR)	SD, OL, PET / oral dose, 1 mg IR PAL (fasting) in healthy males / PK, D_2+ $2HT_{2A}$receptor occupancy, relationship PK-PD. No. Subjects Enrolled: 3 Treated with Paliperidone: 3
R076477-SIV-101 *PET* (ER)	SD, OL, PET in healthy males and females / oral dose, 6 mg (3x2 mg) PAL ER / PK, D_2receptor occupancy, relationship PK-PD. No. Subjects Enrolled: 4 Treated with Paliperidone: 4
R076477-P01-1006 *Food effect in Japanese* (ER)	SD, OL, randomized, 2-way CO in healthy Japanese males and females / oral dose of 3 mg PAL ER (fed or fasting) / food effect in Japanese subjects. No. Subjects Enrolled: 20 Treated with Paliperidone: 20

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005.

Protocol No. (Formulation)	Study Design/Enrollment Status[a]
	PHASE 1/2a STUDIES IN SUBJECTS WITH SCHIZOPHRENIA
R076477-INT-1 *PK in target population* (IR)	MD, OL, randomized, parallel group in subjects with chronic schizophrenia (M/F) / once daily doses of 1, 4, or 8 mg IR PAL / steady-state PK, dose proportionality. No. Subjects Enrolled: 34 Treated with Paliperidone: 34
PAL-SCH-101 *Orthostatic tolerability* (ER)	MD, DB, randomized, PC and AC, parallel group in subjects with schizophrenia (M/F) / placebo on Day 1 and 12 mg/day PAL ER on Days 2-6, 12 mg/day PAL ER on Days 1-6, 2 mg IR RIS on Day 1 and 4 mg/day IR RIS on Days 2-6 / PK, PD (orthostatic hypotension, prolactin), enantiomer disposition. No. Subjects Enrolled: 113 Treated with Paliperidone: 75
R076477-SCH-102 *Dose proportionality and exposure comparison* (ER)	MD, OL, randomized, parallel group in subjects with schizophrenia or schizoaffective disorder (M/F) / 9 mg q.d. PAL ER on Days 8-14 and 15 mg q.d. PAL ER on Days 15-21, dose escalation up to 7 mg b.i.d. IR RIS on Days 8-14 and 8 mg b.i.d. IR RIS on Days 15-21/ dose proportionality, enantiomer disposition, comparison steady-state PK of PAL after PAL treatment *vs.* RIS treatment. No. Subjects Enrolled: 62 Treated with Paliperidone: 36

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005.

Continued on the next page

OTHER PHASE 1/2a STUDIES	
Pharmacodynamic Studies	
R076477-SCH-1010 *Sleep* (ER)	DB, PC, randomized in subjects with schizophrenia-related insomnia (M/F) / 9 mg/day PAL ER, placebo / relationship between PK and PD (sleep architecture). No. Subjects Enrolled: 42 Treated with Paliperidone: 21
R076477-SCH-1009 *Cardiovascular safety* (IR)	DB, PC, AC, randomized in subjects with schizophrenia or schizoaffective disorder (M/F) / placebo on Day 1 and 4 mg q.d. Day 2, 6 mg q.d. Day 3, 8 mg q.d. IR PAL Day 4-8; placebo on Days 1-7 and 400 mg moxifloxacin on Day 8 / influence of paliperidone on ECG parameters, relationship between PK and ECG parameters. No. Subjects Enrolled: 141 Treated with Paliperidone: 72
Studies in Special Populations	
R076477-REI-1001 *Renal impairment* (ER)	SD, OL, parallel group in subjects with severe, moderate and mild renal impairment and with normal renal function (M/F) / oral dose of 3 mg PAL ER (fasting) / plasma and urine PK in renally impaired subjects *vs.* healthy subjects, PPB, enantiomer disposition. No. Subjects Enrolled: 47 Treated with Paliperidone: 47
PALIOROS-SCH-1011 *Elderly PK* (ER)	SD and MD, OL in male and female healthy elderly subjects (> 65 years) and young subjects (18-45 years) / single oral dose of 3 mg PAL ER on Day 1 and 3mg/day PAL ER on Days 6-12 (fasting) / PK in elderly subjects *vs.* young subjects, enantiomer disposition. No. Subjects Enrolled: 60 Treated with Paliperidone: 60

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005.

Continued on the next page

	OTHER PHASE 1/2a STUDIES (continued)
Studies in Special Populations (continued)	SD, OL, parallel group in male and female subjects with moderate hepatic
R076477-SCH-1008 *Hepatic impairment* (IR)	impairment and with normal hepatic functions/ oral dose, 1 mg IR PAL (fasting) SD of PK in subjects with hepatic impairment *vs.* healthy subjects, PPB, enantiomer disposition. No. Subjects Enrolled: 20 Treated with Paliperidone: 20
R076477-P01-1005 *Japanese vs.Caucasian PK* (ER)	SD and MD, DB, PC, randomized in male and female healthy Caucasian and Japanese subjects / SD of 3 mg PAL ER on Day 1, MD of 3 mg/day PAL ER on Days 5-11, and SD 6 mg PAL ER on day 19, placebo (fasting) / SD and MD PK in Japanese subjects *vs.* Caucasians, enantiomer disposition. No. Subjects Enrolled: 60 Treated with Paliperidone: 48
Drug-Drug Interaction Study	
Renal DDI (ER)	R076477-P01-1004 SD, OL, randomized, 2-way crossover in healthy males / single oral dose of 6 mg PAL ER on Day 1, 200 mg trimethoprim b.i.d. on Days 1-8 with single oral dose of 6 mg PAL ER on Day 5 (fasting) / effect of trimethoprim on plasma and urine PK of PAL ER, enantiomer disposition. No. Subjects Enrolled: 30 Treated with Paliperidone: 30

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005.

4.3 Review Strategy

The main focus of this review was on the Summary of Clinical Safety section of the NDA (module 2.7.4) which provides integrated safety of summary information and on the review of sections of the NDA that focus on efficacy results from the placebo controlled, double-blind Phase III trials of Pal that examined efficacy (primarily Studies -303, -304 and -305, as well as the small elderly trial, Study -302).

A special safety study focusing on potential QT interval effects of IR Pal was also reviewed (Study –SCH-1009), since this is a key safety study relevant to assessing the adequate safety of Pal.

The rationale for the review of any additional data (e.g. vital sign information from a Phase study, Study –P01-1005) is provided in the appropriate section of this review where the given study and data is described.

The 120-Day Safety Update Report (SUR) provided updated data from the integrated OL extension trial dataset (and other ongoing trials). Since this longterm OL dataset was the major source for longterm treatment data and met ICH guidelines for 6 and 12 month exposure in this

SUR submission, the focus of the review of this submission was on safety findings from this dataset and on SAEs and ADOs (primarily from the longterm integrated OL dataset). Former, Team Leader Dr. Paul Andreason and the current Team Leader, Dr. Ni Khin concurred with this review strategy.

A number of questions arose during the course of this review that resulted in additional response submissions from the sponsor that came in late in the review cycle. Most of this information has not been reviewed at the time of this writing but will be reviewed either before the PDUFA date for this submission or after receipt of an approvable response (if an approvable action is taken by the Agency on this NDA). Dr. Ni Khin concurred with this review plan regarding the sponsor's responses that were received late in the review cycle.

4.4 Data Quality and Integrity

Reviewer Comments and Conclusions
The following summarizes findings relevant to this section of the review while a more detailed description is provided afterwards:

- *DSI investigation results are pending*
- *Comparisons between CRFs and Narratives (of selected sections and of 3 arbitrarily selected subjects) revealed adequate quality given that Data Correction Forms were included in the CRFs.*

See section 7.2.8 for a discussion of potential concerns with the quality and completeness of the data.

Detailed Description of Comparisons between CRFs and Narratives
The following outlines arbitrarily selected comparisons between narratives and CRFs (comparisons on AE terms were made between the documents to see if any AE terms were deleted or were not accurately described as an AE leading to an ADO or as an SAE):

- Subject 10903 in Study –SCH-1009: had the above described omission in the CRF of whether or not the bradykinesia that lead to early withdrawal was an SAE, but this omission was ultimately found and documented as not being an SAE according to a DCF found in the CRF. This subject was also arbitrarily selected for a comparison between concomitant medications listed in the CRF with those listed in the narrative. The CRF listed Ativan as concomitant drug while mention of this drug was not found in the narrative (either as a brand or generic name). These differences or omissions did not dramatically impact on the overall interpretation of the key observation of bradykinesia, particularly since the DCF was filed with key information.
- Subject 100811 in Study –P01-1008: AEs of drowsiness and nasal congestion were listed in the CRF but could not be found in the narrative. However, these AEs are considered minor deletions with respect to the overall clinical impression of the dystonia that lead to early withdrawal in this subject.

- Subject 300376 in Study -304: The narrative had "drug abuse and "suicidal ideation reported as SAEs on Day 17 but these terms could not be found in the AE section (domain) of the CRF (which had terms of nasal congestion, insomnia and tinea corpis found). However, a DCF found in the CRF of this subject had the following information, as well as additional information that was found in the narrative but not in the AE section (located by a hyperlink to this section) of the CRF that was reviewed:

ORIGINAL

J&J PRD — **DCF 3413 - 0** — Data Correction Form

Trial:	R076477-SCH- 304	Subject:	300376	Subject Initials:	[redacted]
Main Invest:	[redacted]	Book:		Date:	08-Feb-2005
Created By:	[redacted]	Country/site:	USA-03	Sender Name:	[redacted]

Page(s)	Item	Query	Answer/Comment
111	sAE / AE	1)In regards to DCF 3187, you specified the reason for with drawal as other, SAE resulting in hospitalisation : [redacted] However, we can not find an AE with a serious code= YES with hospitalisation in the CRF. According to protocol all hospitalisations require that an SAE form is send to [redacted] Please provide the required info on the adverse event for which the patient withdrew from the study and send an SAE form for the hospitalisation to [redacted] Thank you	Relapse of [specify event] Substance abuse start date = [redacted] stop date = continued. severity = 3 Severe action taken = 4 stopped drug therapy started = ... relation to trail medication = 2 doubtful outcome = continued If applicable: n/a therapy:... start date... end date ..... regimen (or total daily dose in case of RESCUE medication)..... route... given for AE: YES indication:[specify event]..... Report follows this page.

4.5 Compliance with Good Clinical Practices

DSI investigation is underway at the time of this writing.

4.6 Financial Disclosures

This section summarizes financial disclosure information.

Reviewer's comments and conclusions: *Some investigators had financial interest or funding (in at least 2 investigators), while the majority of principal investigators did not have disclosable*

financial information. Approximately 34 sub-investigators were not contacted or did not provide information (as described below). Potential bias in the pivotal Phase III trials was minimized by the study design employed which involved a double-blind, multi-center study design and involved multiple investigators. Sites were also independently monitored. Despite difficulties with contacting sub-investigators, the sponsor generally provided information for the principal investigators, as described below.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The following is key information on pharmacokinetic (PK) properties, as provided by the sponsor:

- Tmax is approximately 24 hours
- The PK of Pal is dose-proportional across the proposed clinical dose range of 3 mg to 12 mg daily.
- T ½ = approximately 23 hours
- Steady state levels are achieved within 4-5 days of daily treatment in most subjects
- Fluctuation indices with daily treatment of 12 mg Pal and 4 mg immediate-release formulation of risperidone are 38% and 125%, respectively, at steady state. See the following figure for comparisons between these drugs on their steady-state concentration profiles (as provided by the sponsor).
- Absolute oral bioavailability is 28%
- Cmax and AUC values increase by 42% and 46%, respectively in a high-fat/high-caloric fed state compared to a fasting state following a SD of 15 mg Pal in healthy subjects confined to bed for 36 hours.
- Plasma protein binding is 74%, primarily to alpha-1-acid glycoprotein and albumin.
- *In vitro* studies show some slight displacement of protein bound Pal to the free fraction (at 50 ng/ml) at high therapeutic concentrations of diazepam, sulfamethazine, warfarin and carbamazepine.
- Administration of radiolabeled IR Pal (1 mg) yields 59% of the dose unchanged in the urine with approximately 80% of radioactivity found in urine and 11% in the feces.
- The following 4 metabolic pathways were identified *in vivo* (accounting for no more than 6.5% of the above 1 mg dose): dealkylation, hydroxylation, dehydrogenation and benzisoxazole scission.
- While *in vitro* studies suggest a role of CYP2D6 and CYP3A4 in Pal metabolism, *in vivo* studies show a limited role of these isozymes.

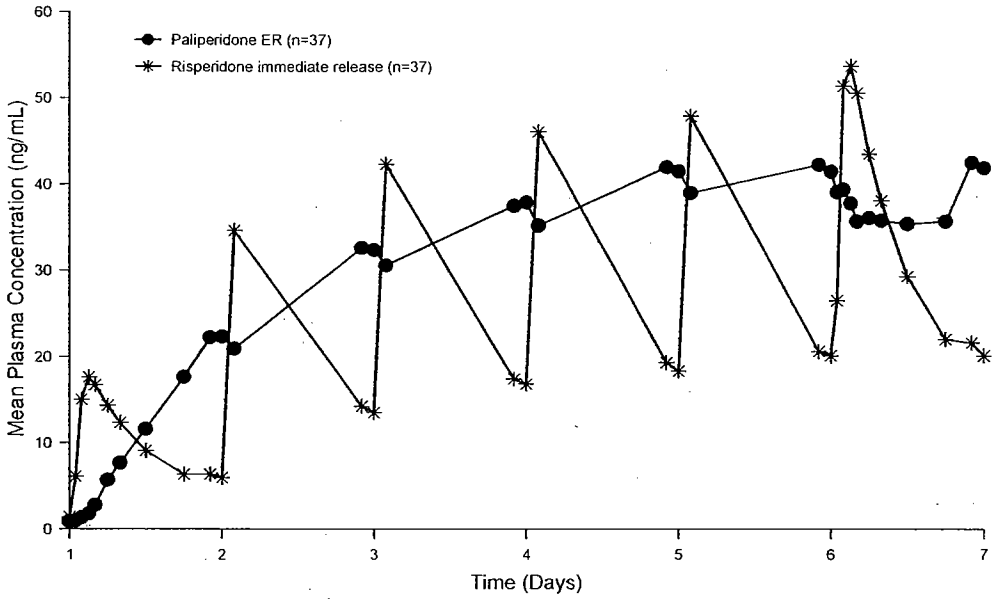


Figure 1.
Steady-state concentration profile following administration of 12 mg paliperidone administered as six 2 mg extended-release tablets once daily for 6 days (paliperidone concentrations are represented) compared with risperidone immediate-release administered as 2 mg once daily on Day 1 and 4 mg once daily on Days 2 to 6 (paliperidone+risperidone concentrations are represented).

As previously listed above, a dramatic food effect on PK was observed in subjects confined to bed for up to 36 hours. The 210-Day SUR provided new results on fed versus fasted effects on PK and examining potential postural effects in the food effect on PK (confined to the bed versus ambulatory). A food effect was demonstrated in both ambulatory and non-ambulatory conditions using the 12 mg single dose-level. The fed state involved a breakfast of 2 eggs, buttered toast (2 pieces), 2 strips of bacon, milk and hash brown fried potatoes before the single morning dose. The figure and table below were copied from the 210-SUR showing key results of this study.

Continued on the next page

Figure 2: Mean Paliperidone Plasma Concentration-Time Profiles After Single-Dose Administration of 12 mg ER OROS Paliperidone in Fed Ambulant, Fasted Ambulant and Fasted Supine Condition
(Study PALIOROS-P01-1012)

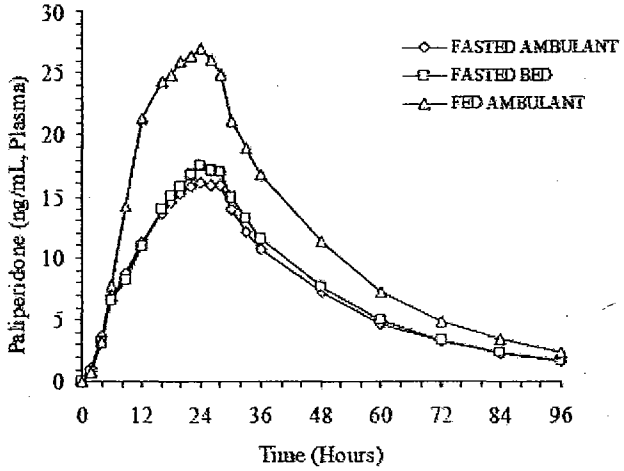


Table 2: Pharmacokinetic Parameters (Mean ± SD) After ER OROS Paliperidone, 12 mg Single Dose
(Study PALIOROS-P01-1012)

PK parameter	Fed, Ambulant[a] (Treatment A)	Fasted, Ambulant[a] (Treatment B)	Fasted, Bed[a] (Treatment C)	Ratio, % (90% CI)[b] A/B	Ratio, % (90% CI)[b] C/B
N	58	59	62	57	57
t_{max}, h	20.00 (9.00 – 28.00)	22.00 (6.00 – 28.00)	24.00 (6.00 – 28.00)	-	-
C_{max}, ng/mL	29.2 ± 15.9	17.4 ± 7.21	18.6 ± 7.59	159.56 (144.21–176.54)	106.08 (95.89–117.36)
AUC_{last}, ng/mL.h	1102 ± 558	685 ± 297	720 ± 303 *	155.51 (140.49–172.13)	103.92 (93.90–115.02)
AUC_{∞}, ng/mL.h	1179 ± 606	741 ± 330	775 ± 331 *	153.94 (139.11–170.36)	103.71 (93.73–114.75)
$t_{1/2}$, h	21.1 ± 3.1	21.9 ± 3.3	21.7 ± 3.3 *	-	-

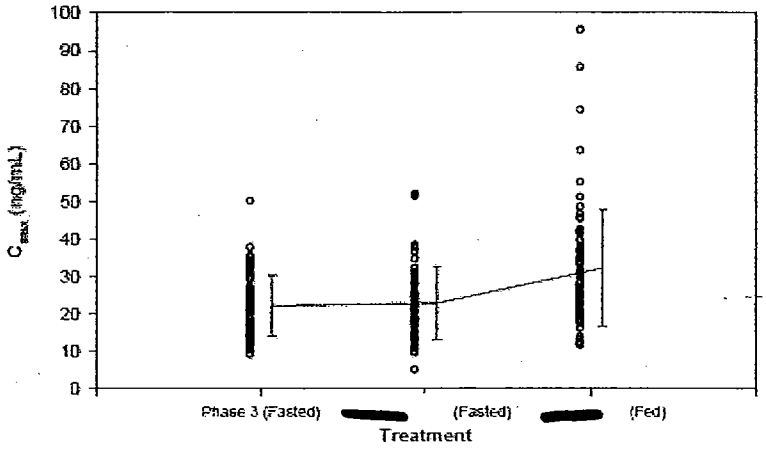
[a] data presented as arithmetic mean ± SD; t_{max} presented as median (range)
[b] ratio of geometric means with 90% confidence intervals; for statistical analysis: data were analyzed on logarithmic scale, and transformed back to original scale
* n=60

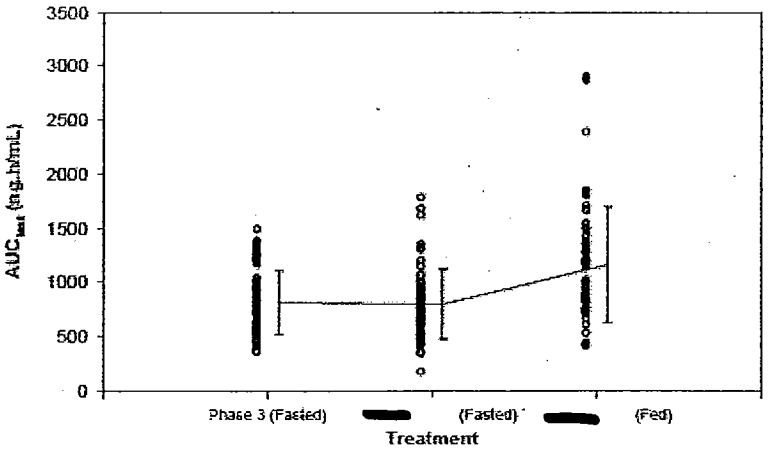
The following figures are of individual subject PK values in the first food effect study conducted which used the 15 mg single dose-level of OROS Pal (Study P01-1008). Subjects were confined to be for up to 36 hours.

Figure PK 5: Individual and Mean Bioavailability Parameters of Paliperidone by Treatment

R076477-P01-1008 page 1 of 2

Treatment A: Single oral dose of 15 mg ER OROS paliperidone Phase 3 formulation in the fasted state
Treatment B: Single oral dose of 15 mg ER OROS paliperidone [redacted] in the fasted state
Treatment C: Single oral dose of 15 mg ER OROS paliperidone [redacted] after a high-fat breakfast
Open circles: individual values ; Solid line: arithmetic mean, SD as error bars





Treatment A: Single oral dose of 15 mg ER OROS paliperidone Phase 3 formulation in the fasted state
Treatment B: Single oral dose of 15 mg ER OROS paliperidone [redacted] in the fasted state
Treatment C: Single oral dose of 15 mg ER OROS paliperidone [redacted] after a high-fat breakfast
Open circles: individual values ; Solid line: arithmetic mean, SD as error bars

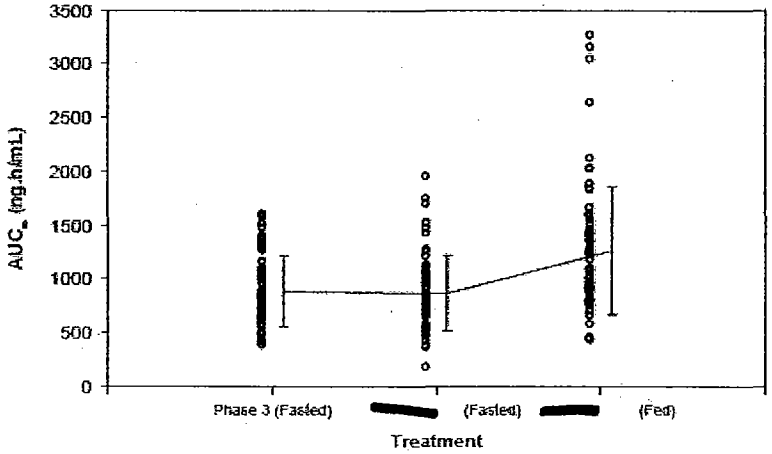


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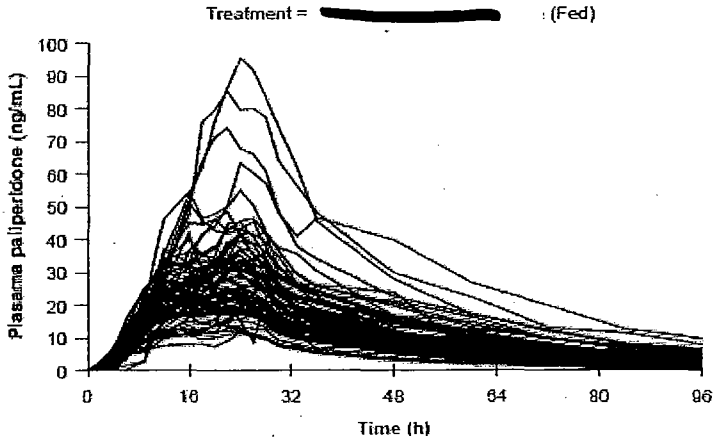
Figure PK 4: Overlay Plasma Concentration-Time Profiles of Paliperidone

R076477-P01-1008 page 3 of 3

Treatment C: Single oral dose of 15 mg ER OROS paliperidone [redacted] after a high-fat breakfast
Top: linear-linear scale ; bottom: log-linear scale



A QT prolongation study will be described later, that showed QT prolongation effects of the immediate release (IR) Pal formulation (Study SCH-1099). However, for comparisons with previously results a figure is shown below of individual subject plasma profiles over treatment days. Before presenting this figure the following outlines treatment given to these subjects (copied from the CSR):

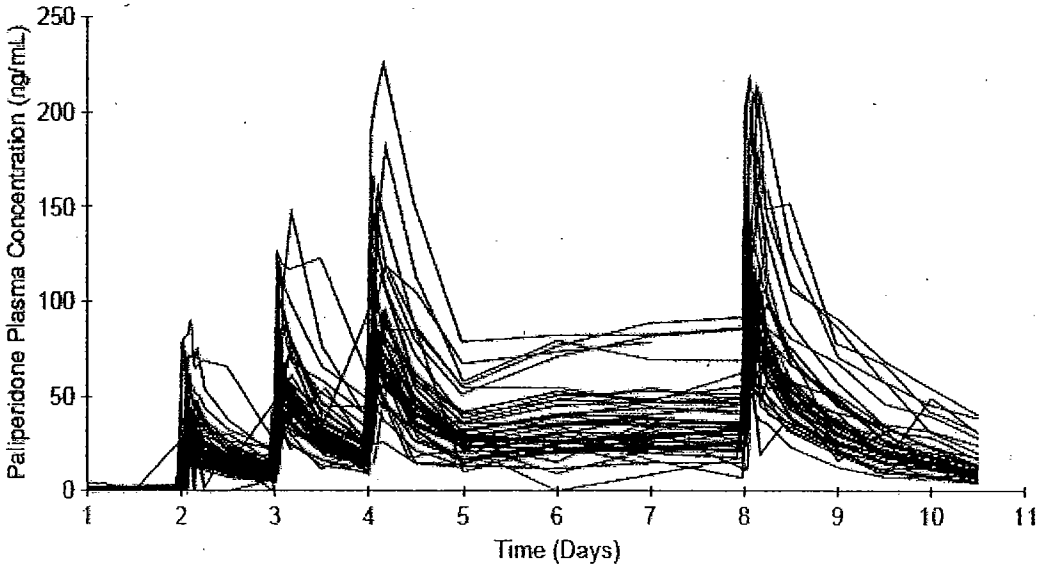
- Four placebo capsules on Day 1;
- Two paliperidone 2 mg capsules and 2 placebo capsules on Day 2;
- Three paliperidone 2 mg capsules and 1 placebo capsule on Day 3;
- Four paliperidone 2 mg capsules on Days 4 through 8.

Subjects in the moxifloxacin group received once daily doses as follows:

- Four placebo capsules on Days 1 to 7;
- One moxifloxacin capsule (over encapsulated 400 mg tablet) and 3 placebo capsules on Day 8.

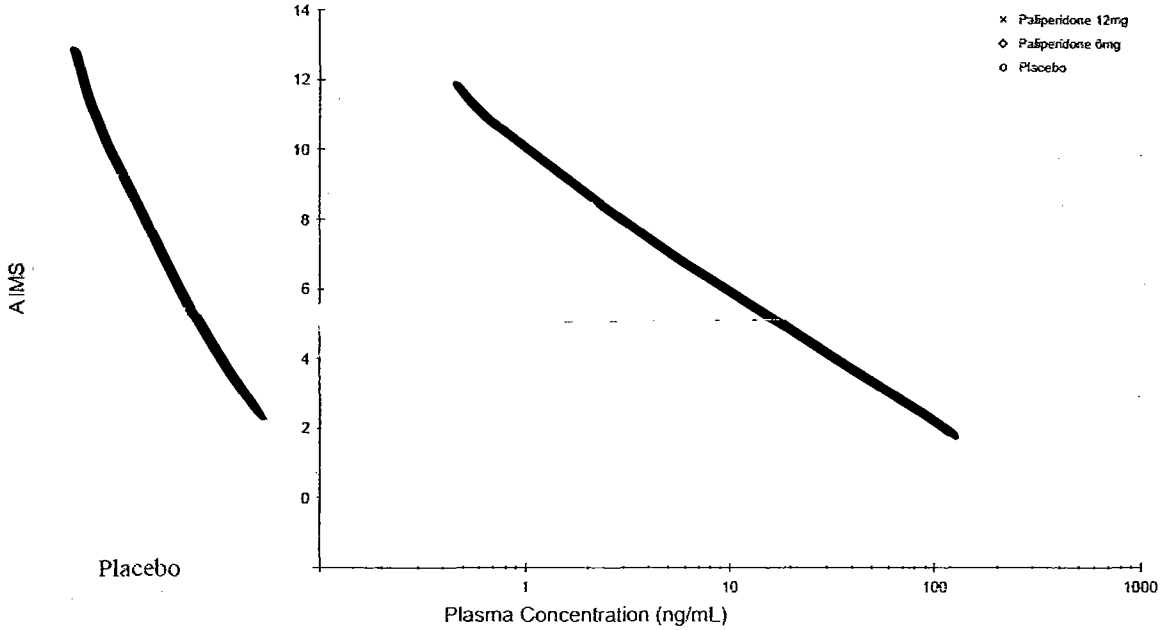
Compare levels from subjects in this QT study (levels are shown in the figure below) to levels shown in previous figures of Pal (OROS formulation) since QT prolongation effects and food effects were observed (Section 7.1.12 A in this review describes QT prolongation results of Study -1009 which was conducted in patients with schizophrenia).

Figure 3: Overlay Plasma Concentration-Time Profiles of Paliperidone on Days 1 through 10 (Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



The following scatterplot is shown (found in the CSR of -304) in order to see the individual subject range of plasma levels observed in subjects in a pivotal 6-week Phase III trial that had the 12 mg daily dose-level. This dose-level is being shown, since the sponsor is recommending this dose as the maximum recommended daily dose in proposed labeling. Dosing was to occur in the mornings in Phase III trials without monitoring food intake and it appears from the protocol description that only the first half of non-elderly subjects, along with all elderly subjects of which there were only a few, were to have PK sampling conducted on selected days (Days 15 and 36 at 1 to 2 hours post-dose and at least 4 hours post-dose). The protocol describes population PK analyses to be conducted on the PK data from Phase III trials.

Figure PKPD 1: Scattterplots of AIMS Versus Plasma Concentration of Paliperidone and Olanzapine
R076477-SCH-304



was preformed prior to administration.
concentrations are represented on a logarithmic scale.
ent: 6 mg ER OROS paliperidone q.d., 12 mg ER OROS paliperidone q.d. or placebo.

PK in Special Populations.

According to the sponsor studies fail to show a need for dose adjustment in patients with hepatic impairments, whereas a reduction in dose is recommended for patients with moderate and severe renal impairment. Dose adjustment is also not needed on the basis of gender or race, according to the sponsor.

Studies of the elderly show a 20% lower clearance rate of Pal at steady state compared to that observed in younger adults (18-45 year olds). However, the sponsor claims that population PK studies failed to reveal a need for dose adjustment.

Reviewer Comment on the Food Effect. *While the above and proposed labeling is subject to OCPB input (pending at this time) the above large food effects of Pal is notable. In the opinion of the undersigned reviewer a food effect is a significant issue from a clinical safety perspective given the cardiovascular effects of the drug as described later in this review. The sponsor includes the following language in labeling regarding this finding:*

[redacted] Clinical trials establishing the safety and efficacy of [redacted] were carried out in subjects without regard to the timing of meals."

The potential for a large food effect exists in the patient population that needs to be adequately characterized in the opinion of the undersigned. Furthermore, proposed labeling (as above) does not in the opinion of the undersigned reviewer, adequately address the issue of a food effect and that the patient population can be subject to this effect. OCPB input is recommended on determining an adequately maximum recommended dose-level and regarding how labeling should describe potential food effects if the NDA were ultimately deemed by the Agency as approved. See the final section of this review for further comment and recommendations.

Reviewer Comment on the Elderly Population. *The sponsor claims a dose adjustment is not needed for elderly yet in the opinion of the undersigned a lower starting dose and a more gradual increase in dose (when clinically indicated) should be recommended for the elderly than is being recommended for the non-elderly healthy patient population, similar to that found in approved labeling for Risperdol,® as described in the following (similar to that found in approved labeling). Refer to the last section of this review for further comment and recommendations.*

[redacted]

Section 7 of this review will describe some safety findings suggestive of an age-group effect among elderly on some of the cardiovascular parameters. This population is also likely to be at greater risk of adverse effects of Pal on not only QT prolongation effects and other cardiovascular effects, but also on adverse effects involving other organ systems. Finally Phase III trials had very few elderly patients and the elderly Study -302 was small, such that safety findings are only considered as preliminary results. Furthermore, subjects in this elderly trial received Pal using a flexible dose design with only 3 mg daily-dose increments permitted in

which the dose could not be increased more frequently at weekly intervals. This is contrasted to the fixed dose Phase III trials of almost all non-elderly adults that used daily doses as high as 15 mg. Therefore, a more gradual dose adjustment as well as a lower starting dose than recommended for the non-elderly population should be recommended in labeling, along with a clear description of the treatment regimen employed in this study and it's limitation in examining safety (primarily due to the small sample size as well as other limitations inherent in the elderly population).

5.2 Pharmacodynamics

The *in vitro* pharmacodynamic properties of Pal (as described in the submission) generally appear to be similar to that of risperidone. Sections on pharmacodynamic properties of Pal on efficacy and safety in clinical trials are addressed later in this review.

5.3 Exposure-Response Relationships

Refer to Sections 6 and 7 for dose-response relationship information on efficacy and safety, respectively.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is for treatment of Schizophrenia.

6.1.1 Methods

Summary of Study Design. Three pivotal multicenter, placebo controlled, active controlled, randomized, double-blind (DB), fixed dose-response, parallel group trials were conducted to establish efficacy of oral paliperidone administration for the treatment of Schizophrenia (Studies R076477-SCH-303, R076477-SCH-304, R076477-SCH-305). The daily doses among these trials ranged from as high as 15 mg daily (in Study R076477-SCH-305) to as low as 3 mg in Study R076477-SCH-303. The 15 mg treatment group was started on 12 mg daily for the first seven days of treatment followed by 15 mg daily for the remainder of the DB phase. The active control groups in these trials received olanzapine (10 mg daily). Double-blind treatment was given for 6 weeks.

The following table summarizes the 3 pivotal efficacy Phase III trials, as well as a summary of a small study of elderly subjects the preliminarily examines efficacy.

Table 2: Phase 3 Multicenter, Double-Blind Placebo-Controlled Studies Providing the Basis of Efficacy for ER OROS Paliperidone in Subjects With Schizophrenia

Protocol No.	Region (Country)	Study Design	Daily Dose and Study Duration	Subjects Included in Analysis of Efficacy
Fixed-Dose Studies in Subjects (≥18 years of age) with Schizophrenia				
R076477-SCH-303 Key Efficacy Study	Western Europe (France, Greece, the Netherlands and Spain) Eastern Europe (Bulgaria, Croatia, Estonia, Poland, Russia, Slovakia) India	Randomized, 6-week DB, placebo- and active-controlled, parallel group, dose-response, 3 fixed dosages of ER OROS paliperidone (6, 9, and 12 mg/day) and olanzapine (10 mg/day).	Placebo ER OROS Paliperidone 6 mg/day 9 mg/day 12 mg/day Olanzapine 10 mg/day 5-day screening 6-wk DB phase	Placebo=126 Paliperidone 6 mg=123 Paliperidone 9 mg=122 Paliperidone 12 mg=129 Olanzapine=128 Total=628
R076477-SCH-304 Key Efficacy Study	United States	Randomized, 6-week DB, placebo- and active-controlled, parallel group, dose-response, 2 fixed dosages of ER OROS paliperidone (6 and 12 mg/day) and olanzapine (10 mg/day).	Placebo ER OROS Paliperidone 6 mg/day 12 mg/day Olanzapine 10 mg/day 5-day screening 6-wk DB phase	Placebo=105 Paliperidone 6 mg=111 Paliperidone 12 mg=111 Olanzapine=105 Total=432
R076477-SCH-305 Key Efficacy Study	North America (United States and Canada) Eastern Europe (Ukraine, Bulgaria, Romania, and Poland) Asia (Hong Kong, Malaysia, Republic of Korea, Singapore, and Taiwan) Israel, Mexico, and South Africa	Randomized, 6-week DB, placebo- and active-controlled, parallel group, dose-response, 3 fixed dosages of ER OROS paliperidone (3, 9, and 15 mg/day) and olanzapine (10 mg/day).	Placebo ER OROS Paliperidone 3 mg/day 9 mg/day 15 mg/day Olanzapine 10 mg/day 5-day screening 6-wk DB phase	Placebo =120 Paliperidone 3 mg=123 Paliperidone 9 mg=123 Paliperidone 15 mg=113 Olanzapine =126 Total=605
Flexible-Dose Safety and Tolerability Study in Elderly Subjects (≥65 years) with Schizophrenia				
R076477-SCH-302 Supportive Efficacy Study	Eastern Europe (Czech Republic, Russia, Slovakia, and Ukraine Other (South Africa and Greece)	Randomized, 6-week DB, placebo-controlled study of flexible doses of ER OROS paliperidone (2:1 ratio of active drug to placebo).	Placebo ER OROS Paliperidone Flexible doses (3 mg to 12 mg/day) 5-day screening 6-wk DB phase	Placebo = 38 Paliperidone 3-12 mg =76 Total =114

Investigators. The sponsor provided a listing of investigators in the N000 submission.

Subjects. A total of 1665 subjects were in the intent-to-treat (ITT) population. The ITT population is defined as a randomized subject who received at least one dose of study drug and had at least one post-randomization efficacy assessment. The following provides an enumeration of ITT subjects by DB study drug assignment (among the 3 pivotal Phase III trials, combined):

- 351 subjects received placebo
- 955 subjects received paliperidone (extended release OROS® formulation)
- 359 subjects received active control drug (10 mg daily of olanzapine)

The following are some of the key eligibility criteria:

- Subjects were 18 years and older adults, generally healthy men and women with Schizophrenia for at least one year using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).
- Subjects were required to have a Positive and negative Symptom Scale total score of 70 to 120 at baseline and were inpatients for at least 14 days during the study.

The following are some key exclusionary criteria:

- Subjects with a history of severe gastrointestinal narrowing were excluded.
- Subjects with a history of failing to respond to risperidone for acute psychosis on at least 2 occasions were excluded (must be documented that failure to respond occurred with adequate doses and durations of treatment or due to failure to tolerate an effective dose).
- Subjects with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values of over twice the upper limit of normal (ULN).

Refer to Sections 4.1 for more details on the enumeration of subjects.

An additional 6-week Phase III trial (R076477-SCH-302) was conducted on elderly patients using a flexible dose design (3-12 mg daily of paliperidone. Other aspects of the study design of this trial were generally similar to that employed in three above described pivotal trials of non-elderly adults. The ITT population consisted of 114 total subjects of which 76 subjects received paliperidone and 38 subjects received placebo. Section 4.1 provides more details enumerating subjects in each treatment group.

Section 6.1.3 describes the actual study design of the above trials in more detail.

Section 6.1.2 describes additional key aspects of the study design of the 6-week DB Phase III trials.

6.1.2 General Discussion of Endpoints

The primary efficacy measure was the mean change from baseline to treatment endpoint on the Positive and negative Symptom Scale (PANSS) total score. This dependent variable is generally considered as a standard measure for Phase III trials for establishing efficacy in treating schizophrenia. Additional comments on the efficacy endpoints are discussed under subsequent sections (or were previously discussed), as well as in the final section of this review which also provides recommendations relevant to efficacy.

6.1.3 Study Design

Section 6.1.1 provides the overall study design and shows a table specifying dose-levels employed. Additional key aspects of the study design of Phase III trials are described below. This section is also intended to include reviewer comments on the study design (in accordance with the Clinical Reviewer MAPP). Sections below that contain reviewer comments are italicized.

Pivotal Phase III Non-Elderly Schizophrenia Trials (Studies -303, -304, and -305)
Screening of subjects occurred within a maximum of 5 days from baseline upon which subjects were randomized to study drug. Daily dose-levels of paliperidone among the 3 pivotal trials were 3, 6, 9, 12 and 15 mg. See previous sections for which studies examined which dose-levels and for the number of subjects in the various treatment groups.

The dose-levels chosen for the pivotal trials were selected on the basis of the following key points, according to the sponsor:

- Risperidone is reported to be equipotent to paliperidone (the basis for this conclusion is not clear to the undersigned reviewer) and the recommended daily dose of risperidone for treatment of schizophrenia is between 2 and 6 mg in approved labeling.
- The mean bioavailability of paliperidone is approximately 33% of that of risperidone, such that a daily dose of 6 to 18 mg of paliperidone was anticipated to be effective, given the 2 to 6 mg daily dose range for risperidone (as above).
- D_2 receptor occupancy of 70 to 80% is hypothesized as being associated with efficacy and was reportedly achieved by doses between 4.5 and 9 mg in a PET scan study conducted as part of the sponsor's development program.

Key eligibility criteria were previously described under Section 6.1.1. One key criterion that is provided in more detail here is that to be eligible for randomization to DB treatment patients had to score within 70-120 on the PANSS total rating at both screening and baseline visits and could not show 25% or greater improvement on the PANSS total score between these 2 visits. Patients who did not meet these criteria were excluded from the study.

Elderly Phase III Trial (Study -302)
This study was almost identical in study design to the previously described pivotal trials except for the follow major differences:

- The age of subjects was restricted to ≥ 65 years old
- Subjects were randomized to either Pal or placebo groups (2:1) for the 6-week DB phase
- A flexible dose regimen was employed at a daily dose-level of 3 to 12 mg of Pal.
- The Pal group started at a daily dose level of 6 mg which could down adjusted to the 3 mg daily dose-level over the first week of DB treatment. However, the daily dose level could not be increased until after the first week of treatment. After the first week of treatment dose increases could be made no more frequently that every 7 days at daily-

dose-level increments of no greater than 3 mg. The dose could be decreased at anytime to a daily dose of no lower than 3 mg. Dose adjustments were made at the clinical discretion of investigators to optimize efficacy, while minimizing adverse effects.

Concomitant medications.
Psychotropic medications were discontinued at screening over a maximum of a 5 day period prior to baseline (prior to randomization to double-blind treatment) and were also prohibited during the DB treatment phase except for the following:

- Patients on a stable dose of benzodiazepines or an antidepressant were continued on their usual regimen during the study at a fixed dose (no dose adjustments were allowed).
- Rescue treatment with benzodiazepines was permitted for agitation, anxiety or sleep difficulties within pre-specified treatment restrictions and
- Rescue benztropine treatment for extrapyramidal symptoms (EPSE) were permitted within pre-specified dosing restrictions.

Section 6.1.4 provides the incidence of the more common concomitant medications used during the study.

Reviewer Comments on the Study Design.
The 6-week duration of the double-blind treatment phase and other aspects of methodology are generally a standard approach for establishing efficacy of a study drug in the treatment of patients with acute schizophrenia. Generally, Phase III trials of this nature only employ a minimum cut-off score on the PANSS total or on a comparable measure. As a result of using this upper limit in the sponsor's Phase III trials, the studies excluded more severely symptomatic patients. Section 6.1.4 shows baseline results that show an adequate proportion of subjects who scored in the severe category on the CGI-S, while few subjects had the highest score on the CGI-S.

[redacted]

Efficacy Assessment Schedule
Efficacy assessments were conducted at screening, baseline, and generally on a weekly basis during the DB phase of each of the 3 pivotal Phase III non-elderly trials and the Phase III elderly trial.

The primary efficacy variable was previously described and further discussion of statistical methods for this variable and secondary variables are provided in the next subsection.

Secondary variables are listed below.

- Mean change from baseline to treatment endpoint in PANSS subscales and on additional scales as follows:

- PANSS subscale for positive symptomatology which includes severity ratings of symptoms that commonly appear in the acute phase such as hallucinations, bizarre behaviors, among others.
- PANSS subscale for negative symptomatology which are severity ratings of symptoms that commonly continue during non-acute (chronic) phases of schizophrenia such as social withdrawal, motor retardation and others.
- Additional PANSS subscales (see Section 6.1.2 for complete listing in a summary table on efficacy results).
- Personal and Social Performance Scale (PSP): a clinician rating scale that has been previously used in psychiatric patients in rehabilitation facilities. Subjects are rated on difficulties in self-care, with work and study, personal and social relationships and aggressive behaviors over a 1-month period. The total score can range from 0 (absent) to a maximum score of 100 (very severe).

- Median change in Clinical Global Impression-Severity Scale (CGI-S) which is a standard scale employed in Phase III trials for examining efficacy in treating a given psychiatric disorder. The clinician rates the overall severity of the patient's psychiatric condition at a given time-point in the study. This scale is intended to provide an overall clinical rating of the severity of the patient's clinical presentation of their psychiatric disorder.
- Visual Analogue Scales (VAS) were employed for self-ratings of quality of sleep and daytime drowsiness, each, over the past 7 nights.
- Additional secondary variables were included.

Table 3: Visit Schedule for Efficacy Assessments Performed in the Four Phase 3 Clinical Studies Providing the Basis of Efficacy for ER OROS Paliperidone in Subjects With Schizophrenia

	Screen	Baseline	Double-Blind Treatment Phase						
Week	-1			1	2	3	4	5	6
Procedures / Day			4	8	15	22	29	36	43
Investigator-Rated Efficacy Assessment									
Positive and Negative Syndrome Scale (PANSS)	X	X	X	X	X	X	X	X	X
Personal and Social Performance Scale (PSP)		X							X
Clinical Global Impression Scale – Severity (CGI-S)		X	X	X	X	X	X	X	X
Subject Self-Rated Efficacy Assessment									
Symptoms and Quality of Life in Schizophrenia Scale (SQLS)		X		X	X		X		X
Sleep Visual Analog Scale (VAS)		X		X	X		X		X

Refer to Table series 10.2 in the appendix of this review for the study schedules for the 3 pivotal, primarily non-elderly trials and for the elderly trial (Studies 303, 304 and 305 and Study 302, respectively).

Reviewer Comment. *A description of key secondary variables cannot be found in efficacy sections of pivotal Phase III trials in Module 2.7.3 (Summary of Clinical Efficacy) or in efficacy sections of the Clinical Study Reports. Documentation of declaring key secondary variables (a priori) cannot be found by the undersigned reviewer or by the Biometrics Reviewer at the time of this writing. Yet the sponsor's proposed labeling includes a description of most secondary*

variables in pivotal trials. Refer to Section 9 for further comment and recommendations on this issue.

Primary and Secondary Efficacy Analyses
The primary efficacy variable was mean change from baseline to treatment endpoint on the Positive and negative Symptom Scale (PANSS) total score.

The primary analysis was conducted on the last-observation-carried-forward (LOCF) dataset of the ITT population (as previously defined). Each paliperidone group was compared to the placebo group on the primary efficacy variable. The statistical test for the primary analyses was an ANCOVA model. Treatment and analysis center were the independent variables in this model and the baseline PANSS total score was a covariate. Dunnett's procedure was used to adjust for multiple comparisons between the placebo group and each paliperidone group. The observed cases (OC) dataset was used for additional secondary analyses for examining effects on the primary efficacy variable at each time-point of the treatment phase.

Each paliperidone group that was found to show "superiority" over placebo on the above primary analyses was also compared on secondary efficacy variables using ANCOVA (on mean change from baseline to treatment endpoint) except for the CGI-S (in which an ANCOVA on the ranks of change was employed). Adjustment for multiple comparisons was conducted by using an unconditional re-sampling algorithm. Treatment group comparisons on the PSP were conducted using this algorithm for adjusting for multiple comparisons. Additionally group comparisons on the PSP were conducted using the Dunnett's procedure.

No adjustments for multiple comparisons were employed for group comparisons on the VAS sleep scores.

6.1.4 Baseline Characteristics of the Study Population (Demographics, Concomitant Medication Use, Medical and Psychiatric Conditions)

Disposition of the Subjects. Refer to Table 4.2.1 in Sections 4.2 above, for enumeration of subjects in various study populations (enrolled, randomized, ITT Safety, completers and others). The disposition of subjects in the 3 pooled pivotal trials is shown in the table below (as copied from the submission).

Continued on the next page

Table 8: Study Completion/Withdrawal Information
(Study R076477-SCH-303: All Randomized Subjects)

	Placebo (N=127) n (%)	ER OROS PAL 6 mg (N=123) n (%)	ER OROS PAL 9 mg (N=122) n (%)	ER OROS PAL 12 mg (N=130) n (%)	Olanzapine 10 mg (N=128) n (%)	Total (N=630) n (%)
Completed	58 (46)	80 (65)	86 (70)	101 (78)	90 (70)	415 (66)
Withdrawn	69 (54)	43 (35)	36 (30)	29 (22)	38 (30)	215 (34)
Lack of efficacy	51 (40)	20 (16)	19 (16)	13 (10)	19 (15)	122 (19)
Subject choice (subject withdrew consent)	7 (6)	9 (7)	11 (9)	8 (6)	5 (4)	40 (6)
Adverse event	9 (7)	8 (7)	4 (3)	8 (6)	9 (7)	38 (6)
Lost to follow-up	2 (2)	1 (1)	2 (2)	0	2 (2)	7 (1)
Death	0	0	0	0	1 (1)	1 (<1)
Study medication non-compliance	0	0	0	0	1 (1)	1 (<1)
Other	0	5 (4)	0	0	1 (1)	6 (1)

Cross-reference: Mod5.3.5.1\R076477-SCH-303\Table 6.

Table 9: Study Completion/Withdrawal Information
(Study R076477-SCH-304: All Randomized Subjects)

	Placebo (N=110) n (%)	ER OROS PAL 6 mg (N=112) n (%)	ER OROS PAL 12 mg (N=112) n (%)	Olanzapine 10 mg (N=110) n (%)	Total (N=444) n (%)
Completed	37 (34)	51 (46)	54 (48)	50 (45)	192 (43)
Withdrawn	73 (66)	61 (54)	58 (52)	60 (55)	252 (57)
Lack of efficacy	39 (35)	26 (23)	16 (14)	24 (22)	105 (24)
Subject choice (subject withdrew consent)	17 (15)	19 (17)	21 (19)	17 (15)	74 (17)
Lost to follow-up	4 (4)	8 (7)	10 (9)	6 (5)	28 (6)
Adverse event	5 (5)	8 (7)	6 (5)	8 (7)	27 (6)
Study medication non-compliance	3 (3)	0	3 (3)	2 (2)	8 (2)
Other	5 (5)	0	2 (2)	3 (3)	10 (2)

Cross-reference: Mod5.3.5.1\R076477-SCH-304\Table 6.

Table 10: Study Completion/Withdrawal Information
(Study R076477-SCH-305: All Randomized Subjects)

	Placebo (N=123) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 9 mg (N=125) n (%)	ER OROS PAL 15 mg (N=115) n (%)	Olanzapine 10 mg (N=128) n (%)	Total (N=618) n (%)
Completed	47 (38)	70 (55)	78 (62)	82 (71)	88 (69)	365 (59)
Withdrawn	76 (62)	57 (45)	47 (38)	33 (29)	40 (31)	253 (41)
Lack of efficacy	54 (44)	31 (24)	23 (18)	14 (12)	16 (13)	138 (22)
Subject choice (subject withdrew consent)	13 (11)	17 (13)	18 (14)	8 (7)	11 (9)	67 (11)
Adverse event	5 (4)	3 (2)	6 (5)	4 (3)	5 (4)	23 (4)
Lost to follow-up	0	1 (1)	0	2 (2)	3 (2)	6 (1)
Study medication non-compliance	0	1 (1)	0	2 (2)	1 (1)	4 (1)
Other	4 (3)	4 (3)	0	3 (3)	4 (3)	15 (2)

Cross-reference: Mod5.3.5.1\R076477-SCH-305\Table 6.

The disposition of subjects in the elderly Phase III trial are shown below (copied from the submission).

Table 5: Study Completion/ Withdrawal Information
(Study R076477-SCH-302 Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)	Total (N=114) n (%)
Completed	26 (68)	64 (84)	90 (79)
Withdrawn	12 (32)	12 (16)	24 (21)
Lack of efficacy	6 (16)	3 (4)	9 (8)
Adverse event	3 (8)	5 (7)	8 (7)
Subject choice (subject withdrew consent)	1 (3)	2 (3)	3 (3)
Death	1 (3)	0	1 (1)
Study medication non-compliance	0	1 (1)	1 (1)
Other[a]	1 (3)	1 (1)	2 (2)

[a] These included discontinuation on Day 36 due to personal circumstances for the subject in the paliperidone group and discontinuation on Day 32 due to lack of study medication at the site for the subject in the placebo group.
Cross-reference: Mod5.3.5.1\R076477-SCH-302\Sec4.1

Demographic Features

Treatment groups among the 3 pivotal trials were generally similar on demographic features (distribution of subjects on the basis of gender or ethnicity and on mean or median age, as well as age range). However, some differences were observed across individual studies, as noted by the sponsor. For example Study -303 (conducted in the US) had a numerically greater distribution of subjects in the overweight or obese categories than in the within-the-normal category compared to the distribution of subjects among these categories in the other 2 trials. Study -303 also had approximately an equal distribution of male and female subjects (52% males), while the other two trials had approximately 70% males. Some differences across ethnic groups were also observed.

Reviewer Comments on Demographic Differences Across Studies. *The differences in demographic features across studies are likely to be reflecting direct or indirect geographical differences in where the studies were conducted, among other factors. Since the observed differences varied from one study to another rather than following a consistent pattern, while efficacy was demonstrated in all 3 trials, as discussed later, it is not likely that demographic differences could account for consistent results on efficacy.*

The study population of each pivotal trial had a mean age of approximately 36 to 39 years old and the majority of subjects were "White" (44 to 69%) and male (59 to 67%). Few subjects in the pivotal trials were elderly (ages ranged from 18 to 76 years old).

The tables below summarize demographic features in pooled studies.

Table 11: Demographic and Baseline Characteristics: Pooled Data
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL					Olanzapine
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg	10 mg
	(N=351)	(N=123)	(N=234)	(N=245)	(N=240)	(N=113)	(N=359)
Age (years)							
N	351	123	234	245	240	113	359
Category, n (%)							
18-25	45 (13)	24 (20)	27 (12)	41 (17)	35 (15)	17 (15)	54 (15)
26-50	253 (72)	84 (68)	173 (74)	174 (71)	173 (72)	84 (74)	256 (71)
>50	53 (15)	15 (12)	34 (15)	30 (12)	32 (13)	12 (11)	49 (14)
Mean (SD)	39.0 (11.04)	36.3 (10.98)	39.4 (10.51)	37.4 (11.18)	38.5 (10.99)	37.6 (9.84)	37.6 (10.94)
Median	39.0	35.0	40.0	36.0	39.5	38.0	37.0
Range	(18;71)	(19;64)	(19;73)	(18;67)	(19;66)	(18;62)	(18;76)
Sex, n (%)							
N	351	123	234	245	240	113	359
Male	231 (66)	78 (63)	137 (59)	151 (62)	146 (61)	73 (65)	240 (67)
Female	120 (34)	45 (37)	97 (41)	94 (38)	94 (39)	40 (35)	119 (33)
Race, n (%)							
N	351	123	234	245	240	113	359
White	217 (62)	61 (50)	152 (65)	170 (69)	156 (65)	50 (44)	215 (60)
Black	79 (23)	25 (20)	64 (27)	22 (9)	65 (27)	27 (24)	85 (24)
Asian	28 (8)	30 (24)	0	28 (11)	0	29 (26)	35 (10)
Other	27 (8)	7 (6)	18 (8)	25 (10)	19 (8)	7 (6)	24 (7)
Region, n (%)							
N	351	123	234	245	240	113	359
North America	147 (42)	40 (33)	111 (47)	45 (18)	111 (46)	37 (33)	150 (42)
Western Europe	33 (9)	21 (17)	15 (6)	34 (14)	17 (7)	17 (15)	36 (10)
Eastern Europe	126 (36)	33 (27)	91 (39)	122 (50)	94 (39)	31 (27)	128 (36)
Asia	45 (13)	29 (24)	17 (7)	44 (18)	18 (8)	28 (25)	45 (13)
Body mass index (kg/m2)							
N	350	123	234	245	240	113	356
Category, n (%)							
Normal <25	168 (48)	68 (55)	90 (38)	137 (56)	104 (43)	61 (54)	178 (50)
Overweight25-<30	93 (27)	30 (24)	75 (32)	77 (31)	81 (34)	25 (22)	95 (27)
Obese >=30	89 (25)	25 (20)	69 (29)	31 (13)	55 (23)	27 (24)	83 (23)
Mean (SD)	26.8 (6.20)	25.7 (5.74)	27.2 (6.34)	25.0 (5.10)	26.8 (6.24)	26.7 (7.71)	26.7 (7.04)
Median	25.7	24.2	26.6	24.4	25.9	24.5	24.9
Range	(16;53)	(15;45)	(15;65)	(16;56)	(13;50)	(17;57)	(15;61)

Continued on the next page

The following table summarizes baseline and past psychiatric history as found in the submission.

Table 12: Diagnosis and Psychiatric History at Baseline: Pooled Data
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL					Olanzapine
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg	10 mg
	(N=351)	(N=123)	(N=234)	(N=245)	(N=240)	(N=113)	(N=359)
Schizophrenia type, n (%)							
N	351	123	234	245	240	113	359
Paranoid (295.30)	281 (80)	90 (73)	204 (87)	195 (80)	199 (83)	85 (75)	299 (83)
Disorganized (295.10)	14 (4)	7 (6)	3 (1)	13 (5)	9 (4)	6 (5)	8 (2)
Catatonic (295.20)	0	1 (1)	1 (<1)	1 (<1)	1 (<1)	1 (1)	1 (<1)
Undifferentiated (295.90)	49 (14)	24 (20)	20 (9)	31 (13)	26 (11)	18 (16)	47 (13)
Residual (295.60)	7 (2)	1 (1)	6 (3)	5 (2)	5 (2)	3 (3)	4 (1)
Age diagnosis of schizophrenia (yrs)							
N	350	121	232	241	240	111	356
Mean (SD)	26.3 (9.57)	25.7 (8.23)	25.8 (8.49)	26.6 (8.49)	25.5 (8.98)	25.2 (7.77)	25.3 (8.74)
Median	24.0	24.0	24.0	24.0	23.0	25.0	23.0
Range	(3;60)	(2;52)	(5;53)	(8;57)	(9;62)	(1;53)	(8;67)
Baseline total PANSS							
N	351	123	234	245	240	113	359
Mean (SD)	93.9 (11.68)	91.6 (12.19)	93.4 (11.20)	93.6 (12.55)	94.4 (11.16)	92.3 (12.33)	93.7 (11.75)
Median	93.0	92.0	92.0	93.0	94.0	91.0	93.0
Range	(70;120)	(71;123)	(70;123)	(67;136)	(70;121)	(65;120)	(67;147)
Baseline CGI-S, n (%)							
N	351	123	234	245	240	113	359
Very mild	1 (<1)	0	0	0	1 (<1)	1 (1)	0
Mild	7 (2)	3 (2)	5 (2)	7 (3)	3 (1)	2 (2)	9 (3)
Moderate	138 (39)	54 (44)	88 (38)	102 (42)	82 (34)	46 (41)	122 (34)
Marked	171 (49)	50 (41)	109 (47)	108 (44)	123 (51)	51 (45)	185 (52)
Severe	34 (10)	16 (13)	32 (14)	26 (11)	31 (13)	13 (12)	41 (11)
Extremely severe	0	0	0	2 (1)	0	0	2 (1)
Prior antipsychotic use, n (%)							
N	351	123	234	245	240	113	359
Atypical antipsychotics	232 (66)	79 (64)	170 (73)	146 (60)	168 (70)	63 (56)	234 (65)
Typical antipsychotics	173 (49)	68 (55)	81 (35)	138 (56)	87 (36)	62 (55)	168 (47)
Prior hospitalization[a], n (%)							
N	351	123	233	245	240	113	358
None	41 (12)	18 (15)	26 (11)	37 (15)	24 (10)	11 (10)	38 (11)
Once	89 (25)	35 (28)	52 (22)	34 (14)	60 (25)	23 (20)	83 (23)
Twice	56 (16)	19 (15)	40 (17)	44 (18)	41 (17)	28 (25)	70 (20)
Three times	47 (13)	20 (16)	35 (15)	39 (16)	41 (17)	15 (13)	46 (13)
Four times or more	118 (34)	31 (25)	80 (34)	91 (37)	74 (31)	36 (32)	121 (34)

[a] Prior hospitalization for psychosis, excluding the current hospitalization.

Table 16: Diagnosis, Psychiatric History, and Symptom Severity at Baseline
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)	15 mg (N=113)	Total (N=963)	10 mg (N=364)
Schizophrenia type, n (%)								
N	355	127	235	246	242	113	963	364
Paranoid (295.30)	285 (80)	93 (73)	205 (87)	195 (79)	201 (83)	85 (75)	779 (81)	304 (84)
Disorganized (295.10)	14 (4)	7 (6)	3 (1)	14 (6)	9 (4)	6 (5)	39 (4)	8 (2)
Catatonic (295.20)	0	1 (1)	1 (<1)	1 (<1)	1 (<1)	1 (1)	5 (1)	1 (<1)
Undifferentiated (295.90)	49 (14)	25 (20)	20 (9)	31 (13)	26 (11)	18 (16)	120 (12)	47 (13)
Residual (295.60)	7 (2)	1 (1)	6 (3)	5 (2)	5 (2)	3 (3)	20 (2)	4 (1)
Age at diagnosis of schizophrenia (yrs)								
N	354	125	233	242	242	111	953	361
Mean (SD)	26.3 (9.57)	25.8 (8.19)	25.8 (8.49)	26.5 (8.56)	25.5 (8.96)	25.2 (7.77)	25.8 (8.51)	25.2 (8.76)
Median	24.0	24.0	24.0	24.0	23.0	25.0	24.0	23.0
Range	(3;60)	(2;52)	(5;53)	(8;57)	(9;62)	(1;53)	(1;62)	(8;67)
Baseline total PANSS								
N	355	127	235	246	242	113	963	364
Mean (SD)	93.8 (11.67)	91.3 (12.14)	93.3 (11.21)	93.7 (12.61)	94.3 (11.18)	92.3 (12.33)	93.3 (11.84)	93.7 (11.73)
Median	93.0	92.0	92.0	93.0	94.0	91.0	93.0	93.0
Range	(70;120)	(71;123)	(70;123)	(67;136)	(70;121)	(65;120)	(65;136)	(67;147)
Baseline CGI-S, n (%)								
N	355	127	235	246	242	113	963	364
Very mild	1 (<1)	0	0	0	1 (<1)	1 (1)	2 (<1)	0
Mild	7 (2)	3 (2)	5 (2)	7 (3)	3 (1)	2 (2)	20 (2)	9 (2)
Moderate	141 (40)	56 (44)	88 (37)	102 (41)	82 (34)	46 (41)	374 (39)	123 (34)
Marked	172 (48)	51 (40)	110 (47)	108 (44)	125 (52)	51 (45)	445 (46)	189 (52)
Severe	34 (10)	17 (13)	32 (14)	27 (11)	31 (13)	13 (12)	120 (12)	41 (11)
Extremely severe	0	0	0	2 (1)	0	0	2 (<1)	2 (1)
Prior antipsychotic use, n (%)								
Atypical antipsychotics	235 (66)	81 (64)	171 (73)	147 (60)	170 (70)	63 (56)	632 (66)	238 (65)
Typical antipsychotics	175 (49)	69 (54)	81 (34)	138 (56)	87 (36)	62 (55)	437 (45)	169 (46)
Prior hospitalization,[a] n (%)								
N	355	127	235	246	242	113	963	364
None	41 (12)	18 (14)	26 (11)	37 (15)	24 (10)	11 (10)	116 (12)	38 (10)
Once	89 (25)	35 (28)	53 (23)	34 (14)	61 (25)	23 (20)	206 (21)	83 (23)
Twice	57 (16)	20 (16)	40 (17)	44 (18)	41 (17)	28 (25)	173 (18)	70 (19)
Three times	48 (14)	22 (17)	35 (15)	40 (16)	42 (17)	15 (13)	154 (16)	48 (13)
Four times or more	120 (34)	32 (25)	81 (34)	91 (37)	74 (31)	36 (32)	314 (33)	125 (34)

[a] Prior hospitalization for psychosis, excluding the current hospitalization.

Reviewer Comment about Severity and Acuity of Schizophrenia in the Study Population.
The sponsor was inquired about the cut-off criteria on the range of allowed PANSS total scores in the eligibility criteria. A N0001 submission responded to an inquiry about the rationale for selected the range of 70-120 that appears to be acceptable in that the population studied appears to consistent of an adequate proportion of acutely ill patients, as described below. Furthermore, statistical methods also included baseline PANSS score as a covariate in the ANCOVA model.

The following explanation for the selection of an upper limit of 120 units on the PANSS was found in the N0001 response submission (dated 1/11/06):

"The upper limit of 120 was chosen to balance the severity of symptoms with the likelihood of the patient being able to provide informed consent."

The following are comments found in section 4.3.1.2 of module 2.5 regarding the acuity and severity of Schizophrenic patients in the 3 primarily non-elderly clinical trials (-303, -304 and -305)

" Both the mean PANSS total scores and the subjects' psychiatric history indicated that the study populations were quite ill. All subjects were currently experiencing an acutepsychotic episode, established by clinical assessment and corroborated by PANSS total scores of 70 to 120, inclusive, after washout of existing antipsychotic medication.
Baseline mean PANSS total scores ranged from 91.6 to 94.4 across the pooled treatment groups, and approximately 60% of subjects (n=994, 60%) were at least markedly ill at randomization as rated by the investigator using the CGI-S. (Mod 2.7.3\Sec 3.1.2) The most common diagnosis among the pooled intent-to-treat analysis set was paranoid schizophrenia (n=1353, 81%), which is consistent with epidemiological data on the relative prevalence of schizophrenia subtypes."

The population included a range of severity in symptomatology with a sufficient proportion of subjects with the "markedly ill" range. Furthermore, the primary analysis included the baseline PANSS score as a covariate in the ANCOVA model. But few subjects were rated as "extremely severe" on the CGI-S. [redacted] *). See the final section of this review for further comment and recommendations.*

Continued on the next page

The following tables summarize demographic and psychiatric baseline information on subjects of the elderly trial, Study -302 (copied from the CSR).

Table 7: Demographic and Baseline Characteristics
(Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)	Total (N=114)
Age (years)			
N	38	76	114
Category, n (%)			
64-69	23 (61)	43 (57)	66 (58)
70-75	13 (34)	19 (25)	32 (28)
>75	2 (5)	14 (18)	16 (14)
Mean (SD)	69.1 (3.34)	70.1 (4.95)	69.7 (4.49)
Median	68.0	68.0	68.0
Range	(65;76)	(64;81)	(64;81)
Sex, n (%)			
N	38	76	114
Male	11 (29)	20 (26)	31 (27)
Female	27 (71)	56 (74)	83 (73)
Race, n (%)			
N	38	76	114
White	38 (100)	75 (99)	113 (99)
Other	0	1 (1)	1 (1)
Ethnicity, n (%)			
N	38	76	114
Neither Hispanic/Latino nor Native Amer.	38 (100)	76 (100)	114 (100)
Weight (kg)			
N	38	76	114
Mean (SD)	66.8 (10.22)	65.6 (12.94)	66.0 (12.07)
Median	68.0	64.8	66.1
Range	(44;89)	(45;101)	(44;101)
Height (cm)			
N	38	76	114
Mean (SD)	162.1 (7.38)	161.6 (9.05)	161.7 (8.50)
Median	162.3	162.0	162.0
Range	(137;175)	(145;180)	(137;180)
Body mass index (kg/m^2)			
N	38	76	114
Category, n (%)			
Normal <25	19 (50)	45 (59)	64 (56)
Overweight 25-<30	13 (34)	19 (25)	32 (28)
Obese >=30	6 (16)	12 (16)	18 (16)
Mean (SD)	25.6 (4.87)	25.2 (5.15)	25.3 (5.04)
Median	25.0	24.2	24.4
Range	(17;41)	(17;43)	(17;43)

Table 8: Diagnosis and Psychiatric History at Baseline
(Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)	Total (N=114)
Schizophrenia type, n (%)			
N	38	76	114
Paranoid (295.30)	33 (87)	64 (84)	97 (85)
Disorganized (295.10)	1 (3)	1 (1)	2 (2)
Catatonic (295.20)	0	1 (1)	1 (1)
Undifferentiated (295.90)	2 (5)	3 (4)	5 (4)
Residual (295.60)	2 (5)	7 (9)	9 (8)
Age at diagnosis of schizophrenia (yrs)			
N	36	71	107
Mean (SD)	38.8 (11.71)	37.3 (13.71)	37.8 (13.04)
Median	37.5	34.0	36.0
Range	(21;66)	(13;71)	(13;71)
Baseline PANSS total score			
N	38	76	114
Mean (SD)	94.3 (9.00)	91.8 (9.69)	92.6 (9.50)
Median	93.0	92.5	93.0
Range	(79;117)	(75;119)	(75;119)
Baseline CGI-S, n (%)			
N	38	76	114
Mild	0	1 (1)	1 (1)
Moderate	16 (42)	31 (41)	47 (41)
Marked	18 (47)	40 (53)	58 (51)
Severe	4 (11)	4 (5)	8 (7)
Prior psychotropic use, n (%)			
N	38	76	114
Yes	37 (97)	71 (93)	108 (95)
No	1 (3)	5 (7)	6 (5)
Prior hospitalization*, n (%)			
N	38	76	114
None	2 (5)	3 (4)	5 (4)
Once	5 (13)	3 (4)	8 (7)
Twice	4 (11)	11 (14)	15 (13)
Three times	7 (18)	8 (11)	15 (13)
Four times or more	20 (53)	51 (67)	71 (62)

* Prior hospitalization for psychosis, excluding the current hospitalization.

Study Drug Exposure. This topic is discussed in Section 7 on safety.

Conconmitant Medication Use.
10% of subjects in the pooled Phase III efficacy trails (-303, -304 and -305) continued antidepressant medication. Treatment groups were generally comparable on previous psychotroptic medication such that subjects were also comparable on psychotropic medications discontinued according to the protocol (based on in-text description of results in section 1.4.2.1. of Module 2.7.4).

The incidence of rescue medication use within a give treatment group generally ranged from as low as 54% to as high as 78% across the 3 pivotal trials. Lorazepam was the most commonly used rescue medication. A clear relationship between dose of paliperidone and use of rescue

medications was not revealed by the sponsor (based on in-text description of results in section 1.4.2.1. of Module 2.7.4).

Anticholinergic agents were the most frequently used drug for treatment of EPSEs in which 12% to 19% of subjects in a given treatment group received anticholinergic treatment during the DB trials, pooled.

The table below summarizes the incidence of use of other concomitant medications in the study.

Table 21: Other Concomitant Medication Received During the Double-Blind Phase in ≥ 5% of Subjects in Any Treatment Group
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

Generic Term Category	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
No. subjects with any concomitant therapy	201 (57)	66 (52)	137 (58)	128 (52)	164 (68)	66 (58)	561 (58)	192 (53)
Paracetamol	70 (20)	18 (14)	50 (21)	37 (15)	61 (25)	18 (16)	184 (19)	58 (16)
Ibuprofen	34 (10)	5 (4)	20 (9)	12 (5)	26 (11)	7 (6)	70 (7)	29 (8)
Biperiden	11 (3)	4 (3)	7 (3)	29 (12)	23 (10)	6 (5)	69 (7)	12 (3)
Benzatropine	16 (5)	6 (5)	10 (4)	8 (3)	20 (8)	8 (7)	52 (5)	12 (3)
Maalox	14 (4)	5 (4)	7 (3)	4 (2)	12 (5)	3 (3)	31 (3)	15 (4)
Magnesium	12 (3)	3 (2)	8 (3)	7 (3)	7 (3)	6 (5)	31 (3)	14 (4)
Trihexyphenidyl	6 (2)	3 (2)	2 (1)	12 (5)	7 (3)	6 (5)	30 (3)	6 (2)
Metformin	14 (4)	3 (2)	5 (2)	6 (2)	13 (5)	1 (1)	28 (3)	4 (1)
Propranolol	7 (2)	4 (3)	6 (3)	4 (2)	3 (1)	8 (7)	25 (3)	4 (1)
Diphenhydramine	13 (4)	2 (2)	11 (5)	0	6 (2)	1 (1)	20 (2)	11 (3)

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Appendix 2.7.4.2.5.1.

In the elderly Study -302, the following tables show the mot commonly used rescue medications and concomitant use of antidepressant medications among the subjects (copied from the submission).

Table 9: Duration (Days) of The Most Frequently Used Rescue Medication Received During the Double-Blind Phase
(Study R076477-SCH-302: Safety Analysis Set)

	N	Mean	SD	Med	Min	Max
Rescue Medication						
DIAZEPAM						
Placebo	3	7.0	2.00	7.0	5	9
ER OROS PAL	11	5.5	4.11	5.0	1	13
LORAZEPAM						
Placebo	7	4.7	4.75	3.0	1	14
ER OROS PAL	6	14.3	14.31	10.5	3	41

Table 10: Antidepressant Medications Received During the Double-Blind Phase (Study R076477-SCH-302: Safety Analysis Set)

Medication Generic Term	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)	Total (N=114) n (%)
Total no. subjects with any antidepressant medication	0	10 (13)	10 (9)
Amitriptyline	0	6 (8)	6 (5)
Sertraline	0	2 (3)	2 (2)
Mirtazapine	0	1 (1)	1 (1)
Venlafaxine hydrochloride	0	1 (1)	1 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.

68% of placebo subjects and 61% of Pal subjects used other concomitant drugs in the elderly Study -302. The following drugs were the most commonly used among all subjects (used in over 5% of all subjects):

- Biperiden (17% of all subjects)
- Biperiden hydrochloride (5% of all subjects)
- Aspirin (7% of all subjects)
- Furosemide (6% of all subjects).

Concomitant Illness. The following table shows the incidence of specified major medical conditions as shown by the sponsor.

Table 15: Demographic and Baseline Characteristics (continued)
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo	ER OROS PAL 3 mg	ER OROS PAL 6 mg	ER OROS PAL 9 mg	ER OROS PAL 12 mg	ER OROS PAL 15 mg	Total Paliperidone	Olanzapine 10 mg
Does subject currently smoke?, n (%)								
N	355	127	234	346	242	113	963	364
Yes	224 (63)	66 (52)	152 (65)	128 (52)	162 (67)	62 (55)	570 (59)	237 (65)
No	131 (37)	61 (48)	82 (35)	118 (48)	80 (33)	51 (45)	392 (41)	127 (35)
Diabetes, n (%)								
N	355	127	235	346	242	113	963	364
Yes	18 (5)	4 (3)	9 (4)	8 (3)	17 (7)	3 (3)	41 (4)	11 (3)
No	337 (95)	123 (97)	226 (96)	238 (97)	225 (93)	110 (97)	922 (96)	353 (97)
Hypertension, n (%)								
N	355	127	235	346	242	113	963	364
Yes	46 (13)	7 (6)	28 (12)	17 (7)	28 (12)	14 (12)	94 (10)	35 (10)
No	309 (87)	120 (94)	207 (88)	229 (93)	214 (88)	99 (88)	869 (90)	329 (90)
Dyslipidemia, n (%)								
N	355	127	235	346	242	113	963	364
Yes	18 (5)	4 (3)	8 (3)	9 (4)	11 (5)	6 (5)	38 (4)	12 (3)
No	337 (95)	123 (97)	227 (97)	237 (96)	231 (95)	107 (95)	925 (96)	352 (97)
Cardiovascular disease, n (%)								
N	355	127	235	346	242	113	963	364
Yes	8 (2)	3 (2)	4 (3)	3 (1)	6 (3)	3 (3)	18 (2)	6 (2)
No	347 (98)	124 (98)	231 (98)	243 (99)	236 (98)	111 (98)	945 (98)	358 (98)

The following table is regarding Study -302.

Table 7: Demographic and Baseline Characteristics (Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)	Total (N=114)
Current smoker, n (%)			
N	37	76	113
Yes	10 (27)	20 (26)	30 (27)
No	27 (73)	56 (74)	83 (73)
Diabetes, n (%)			
N	38	76	114
Yes	3 (8)	11 (14)	14 (12)
No	35 (92)	65 (86)	100 (88)
Hypertension, n (%)			
N	38	76	114
Yes	11 (29)	29 (38)	40 (35)
No	27 (71)	47 (62)	74 (65)
Dyslipidemia, n (%)			
N	38	76	114
Yes	0	2 (3)	2 (2)
No	38 (100)	74 (97)	112 (98)
Cardiovascular disease, n (%)			
N	38	76	114
Yes	17 (45)	32 (42)	49 (43)
No	21 (55)	44 (58)	65 (57)

Cross-reference: Attachments 2.1.1 and 2.1.2.

6.1.5 Efficacy Findings

Each pivotal Phase III trial (Studies R076477-SCH-303, R076477-SCH-304, R076477-SCH-305) was positive for efficacy on the primary efficacy variable (mean change from baseline to treatment endpoint on the PANNS-total score).

Results of the primary and secondary efficacy variables form each trial is shown below (copied from the submission).

Continued on the next page

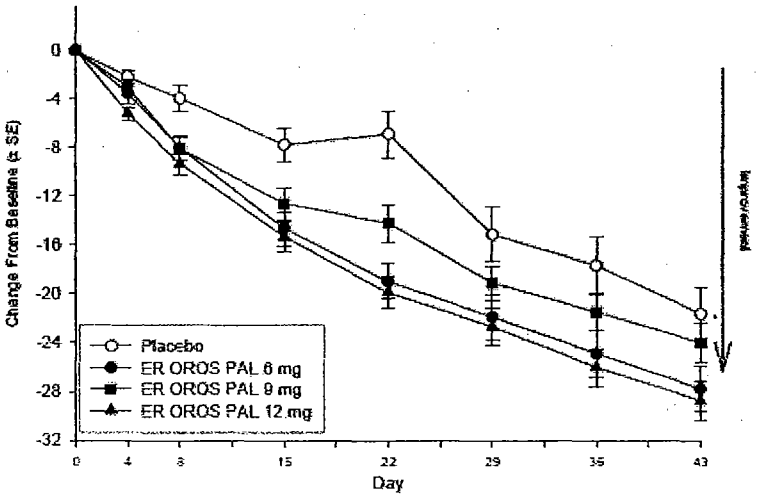
Table 4: Overview of Efficacy Change From Baseline to End Point LOCF Results for Study R076477-SCH-303: Intent-to-Treat Analysis Set

Efficacy Variable	Placebo (N=126)	ER OROS PAL 6 mg (N=123)	ER OROS PAL 9 mg (N=122)	ER OROS PAL 12 mg (N=129)
PANSS total score (primary variable) (n)	126	123	122	129
Mean change (SD)	-4.1 (23.16)	-17.9 (22.23)*	-17.2 (20.23)*	-23.3 (20.12)*
PSP (n)	120	119	118	129
Mean change (SD)	0.5 (15.51)	9.1 (15.52)*,#	8.1 (14.46)*,#	11.5 (15.98)*,#
CGI-S (n)	126	122	122	129
Median change (Range)	0.0 (-4;2)	-1.0 (-4;2)#	-1.0 (-4;1)#	-1.0 (-5;1)#
SQLS (n)	120	120	120	121
Mean change (SD)	-4.9 (16.64)	-8.3 (14.75)	-12.9 (17.92)#	-13.4 (18.95)#
PANSS Factor Scores (n)	126	123	122	129
Mean change (SD)				
Positive symptoms	-2.1 (6.98)	-6.6 (7.40)†	-6.2 (6.87)†	-8.2 (6.64)†
Negative symptoms	-1.0 (5.85)	-4.2 (6.17)†	-3.5 (5.43)†	-5.0 (5.98)†
Disorganized thoughts	-0.9 (5.70)	-3.5 (5.05)†	-3.1 (4.73)†	-4.6 (5.14)†
Uncontrolled hostility/excitement	0.5 (4.48)	-1.4 (4.28)†	-1.8 (3.83)†	-2.4 (3.44)†
Anxiety/depression	-0.6 (3.97)	-2.1 (3.29)†	-2.6 (3.42)†	-3.0 (3.38)†
Quality of Sleep (n)	119	121	120	126
Mean change (SD)	1.0 (35.49)	13.5 (33.84)†	10.5 (31.21)†	12.2 (32.54)†
Daytime Drowsiness (n)	119	121	120	126
Mean change (SD)	-5.8 (30.26)	-2.4 (24.27)	-7.2 (30.73)	-6.4 (29.88)

* Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using Dunnett's procedure to adjust for multiple comparisons.
# Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using unconditional randomization resampling algorithm to adjust for multiple comparisons.
† Denotes a statistically significant ($p<0.05$) improvement with no adjustment for multiple comparisons.
Note: A comparison between the olanzapine 10 mg group and the ER OROS paliperidone groups in terms of the primary efficacy variable showed no statistically significant between-group differences.
Cross-reference: Mod5.3.5.1\R076477-SCH-303\Synopsis Efficacy Results.

Continued on the next page

Figure 7: Change From Baseline in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score Over Time – Observed Case (Study R076477-SCH-303: Intent-to-Treat Analysis Set)



Placebo:	125	123	114	109	73	54	58
PAL 6 mg:	123	116	119	101	90	83	81
PAL 9 mg:	121	117	110	106	91	87	86
PAL 12 mg:	128	122	123	121	106	97	90

Cross-reference: Attachment 5.1.1

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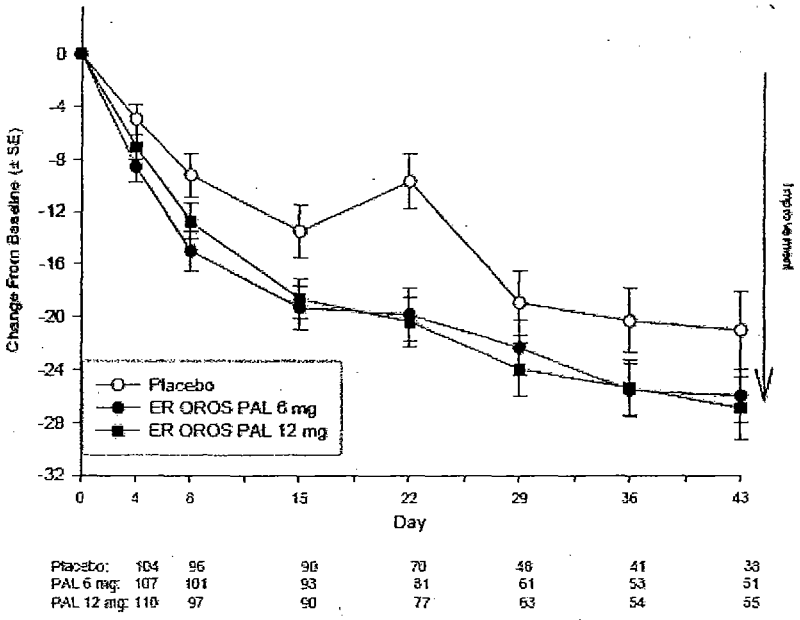
Table 5: Overview of Efficacy Change From Baseline to End Point LOCF Results for Study R076477-SCH-304: Intent-to-Treat Analysis Set

Efficacy Variable	Placebo (N=105)	ER OROS PAL 6 mg (N=111)	ER OROS PAL 12 mg (N=111)
PANSS total score (primary variable) (n)	105	110	111
Mean change (SD)	-8.0 (21.48)	-15.7 (18.89)*	-17.5 (19.83)*
PSP (n)	88	93	91
Mean change (SD)	2.9 (13.04)	8.8 (13.92)*,#	6.6 (13.06)
CGI-S (n)	105	111	111
Median change (Range)	0.0 (-4;2)	-1.0 (-4;1)#	-1.0 (-3;1)#
SQLS (n)	100	107	107
Mean change (SD)	-3.3 (16.31)	-6.7 (16.62)	-5.7 (14.19)
PANSS Factor Scores (n)	105	111	111
Mean change (SD)			
Positive symptoms	-2.9 (7.07)	-5.2 (5.95)†	-6.0 (6.68)†
Negative symptoms	-2.2 (6.59)	-4.4 (5.87)†	-3.9 (5.56)†
Disorganized thoughts	-1.7 (5.13)	-2.7 (4.33)	-3.7 (4.98)†
Uncontrolled hostility/excitement	0.3 (3.90)	-1.2 (3.92)†	-1.5 (3.91)†
Anxiety/depression	-1.5 (4.36)	-2.3 (3.67)	-2.4 (3.75)
Quality of Sleep (n)	101	106	107
Mean change (SD)	-3.3 (36.16)	8.3 (33.40)†	6.8 (35.03)†
Daytime Drowsiness (n)	101	107	107
Mean change (SD)	-3.6 (29.93)	0.9 (31.57)	1.2 (31.96)

* Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using Dunnett's procedure to adjust for multiple comparisons.
# Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using unconditional randomization resampling algorithm to adjust for multiple comparisons.
† Denotes a statistically significant ($p<0.05$) improvement with no adjustment for multiple comparisons.
Note: A comparison between the olanzapine 10 mg group and the ER OROS paliperidone groups in terms of the primary efficacy variable showed no statistically significant between-group differences.
Cross-reference: Mod5.3.5.1\R076477-SCH-304\Synopsis Efficacy Results.

Figure 7: Change From Baseline in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score Over Time – Observed Case
(Study R076477-SCH-304: Intent-to-Treat Analysis Set)



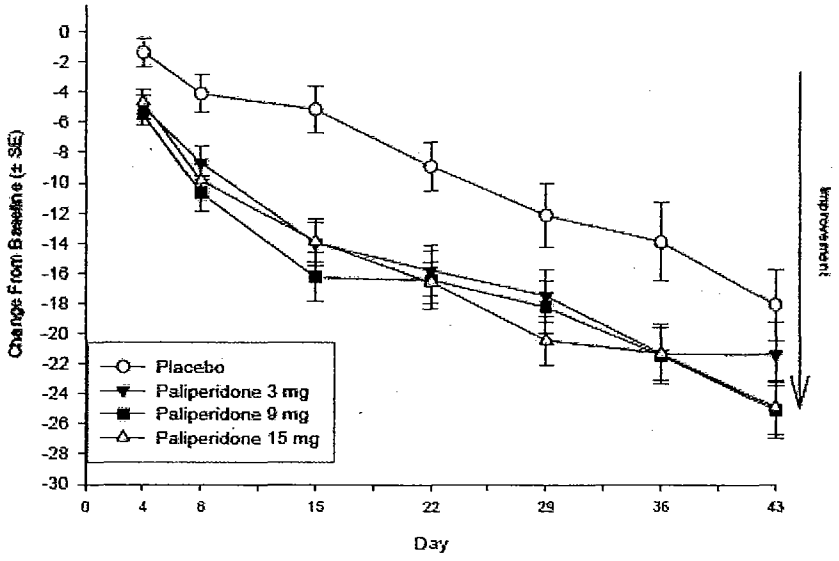
Cross-reference: Attachment 5.1.1

Table 6: Overview of Efficacy Change From Baseline to End Point LOCF Results for Study R076477-SCH-305: Intent-to-Treat Analysis Set

Efficacy Variable	Placebo (N=120)	ER OROS PAL 3 mg (N=123)	ER OROS PAL 9 mg (N=123)	ER OROS PAL 15 mg (N=113)
PANSS total score (primary variable) (n)	120	123	123	112
Mean change (SD)	-2.8 (20.89)	-15.0 (19.61)[*]	-16.3 (21.81)[*]	-19.9 (18.41)[*]
PSP (n)	109	113	116	107
Mean change (SD)	-1.5 (15.82)	8.3 (17.11)[*,#]	7.6 (14.20)[*,#]	12.2 (15.65)[*,#]
CGI-S (n)	120	123	123	113
Median change (Range)	0.0 (-5;2)	-1.0 (-4;1)[#]	-1.0 (-4;2)[#]	-1.0 (-5;1)[#]
SQLS (n)	114	116	116	112
Mean change (SD)	-3.8 (13.40)	-7.4 (14.77)[#]	-6.7 (15.93)	-7.5 (16.45)
PANSS Factor Scores (n)	120	123	123	113
Mean change (SD)				
Positive symptoms	-2.1 (6.90)	-5.0 (6.89)[†]	-6.0 (7.74)[†]	-6.9 (6.87)[†]
Negative symptoms	-1.0 (5.52)	-3.8 (5.27)[†]	-3.9 (5.36)[†]	-4.2 (5.30)[†]
Disorganized thoughts	-0.2 (5.34)	-3.4 (5.06)[†]	-3.4 (5.47)[†]	-3.9 (4.46)[†]
Uncontrolled hostility/excitement	1.2 (4.68)	-1.1 (3.61)[†]	-1.2 (4.48)[†]	-2.3 (3.34)[†]
Anxiety/depression	-0.7 (3.46)	-1.8 (3.35)[†]	-1.9 (3.72)[†]	-2.6 (2.87)[†]
Quality of Sleep (n)	115	118	120	113
Mean change (SD)	3.6 (35.99)	9.0 (34.52)	12.3 (34.88)[†]	11.3 (33.17)
Daytime Drowsiness (n)	115	118	119	113
Mean change (SD)	-0.5 (29.69)	-2.9 (28.10)	-0.9 (33.85)	-3.8 (34.47)

[*] Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using Dunnett's procedure to adjust for multiple comparisons.
[#] Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using unconditional randomization resampling algorithm to adjust for multiple comparisons.
[†] Denotes a statistically significant ($p<0.05$) improvement with no adjustment for multiple comparisons.
A comparison between the olanzapine 10 mg group and the ER OROS paliperidone groups in terms of the primary efficacy variable showed no statistically significant between-group differences.
Cross-reference: Mod5.3.5.1\R076477-SCH-305\Synopsis Efficacy Results.

Figure 7: Change From Baseline in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score Over Time – Observed Case (Study R076477-SCH-305: Intent-to-Treat Analysis Set)



Placebo:	118	111	99	90	87	49	47
PAL 3 mg:	122	119	112	105	82	78	70
PAL 9 mg:	122	114	108	108	95	85	77
PAL 15 mg:	112	108	105	102	91	84	82

Cross-reference: Attachment 5.1.1

The study of elderly patients (Study -302) showed numerical trends for greater improvement on the PANSS-total score in the Pal group than observed in the placebo group as shown in the summary table and figure below (copied from the submission).

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Table 15: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Change From Baseline to End Point-LOCF (Study R076477-SCH-302: Intent-to-Treat Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)
Baseline		
N	38	76
Mean (SD)	94.3 (9.00)	91.8 (9.69)
Median (Range)	93.0 (79;117)	92.5 (75;119)
End point		
N	38	76
Mean (SD)	84.4 (14.55)	77.3 (14.98)
Median (Range)	84.0 (46;119)	76.5 (44;122)
Change from Baseline		
N	38	76
Mean (SD)	-9.9 (15.00)	-14.6 (14.64)
Median (Range)	-8.5 (-39;26)	-14.5 (-44;22)
Diff. of LS Means (SE) [a,b]		-5.5 (2.20)
95% CI		(-9.85;-1.12)

[a] Analysis of covariance from ANCOVA model with factors for treatment, age group and analysis center, and with baseline value as a covariate.
[b] Comparison with Placebo
Note: Negative change in score indicates improvement.

The following figure shows results on the primary variable by dose-level for each of the 3 short-term pivotal trials and for pooled data (as copied from the submission).

Table 18: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point-LOCF for Each Study and the Pooled Data (Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305): Intent-to-Treat Analysis Set)

		ER OROS PAL			
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
R076477-SCH-303	(N=126)		(N=123)	(N=122)	(N=129)	
N	126		123	122	129	
Mean baseline (SD)	94.1 (10.74)		94.3 (10.48)	93.2 (11.90)	94.6 (10.98)	
Mean change (SD)	-4.1 (23.16)		-17.9 (22.23)	-17.2 (20.23)	-23.3 (20.12)	
P-value (vs. Placebo)[a,b]			<0.001	<0.001	<0.001	
Diff. of LS Means (SE)			-13.7 (2.63)	-13.5 (2.63)	-18.9 (2.60)	
95% CI			(-19.91;-7.53)	(-19.65;-7.25)	(-25.07;-12.82)	
R076477-SCH-304	(N=105)		(N=111)		(N=111)	
N	105		110		111	
Mean baseline (SD)	93.6 (11.71)		92.3 (11.96)		94.1 (11.42)	
Mean change (SD)	-8.0 (21.48)		-15.7 (18.89)		-17.5 (19.83)	
P-value (vs. Placebo)[a,b]			0.006		<0.001	
Diff. of LS Means (SE)			-7.0 (2.36)		-8.5 (2.35)	
95% CI			(-12.27;-1.81)		(-13.75;-3.32)	
R076477-SCH-305	(N=120)	(N=123)		(N=123)		(N=113)
N	120	123		123		112
Mean baseline (SD)	93.9 (12.66)	91.6 (12.19)		93.9 (13.20)		92.4 (12.36)
Mean change (SD)	-2.8 (20.89)	-15.0 (19.61)		-16.3 (21.81)		-19.9 (18.41)
P-value (vs. Placebo)[a,b]		<0.001		<0.001		<0.001
Diff. of LS Means (SE)		-11.6 (2.35)		-12.9 (2.34)		-17.2 (2.40)
95% CI		(-17.17;-6.09)		(-18.42;-7.38)		(-22.82;-11.51)

Table, continued.

Table 18: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point-LOCF for Each Study and the Pooled Data (Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305): Intent-to-Treat Analysis Set)

		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
Pooled Data: Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305						
	(N=351)	(N=123)	(N=234)	(N=245)	(N=240)	(N=113)
N	351	123	233	245	240	112
Mean baseline (SD)	93.9 (11.68)	91.6 (12.19)	93.4 (11.22)	93.6 (12.55)	94.4 (11.16)	92.4 (12.36)
Median baseline (Range)	93.0(70;120)	92.0 (71;123)	92.0 (70;123	93.0 (67;136)	94.0 (70;121)	91.0 (65;120)
Mean end point (SD)	89.1 (24.59)	76.6 (21.08)	76.5 (21.04)	76.8 (22.18)	73.7 (20.47)	72.5 (19.12)
Median end point (Range)	90.0 (30;164)	76.0 (30;140)	74.0 (30;138)	75.0 (30;176)	71.0 (31;157)	72.0 (30;121)
Mean change (SD)	-4.8 (21.95)	-15.0 (19.61)	-16.9 (20.70)	-16.8 (21.00)	-20.6 (20.15)	-19.9 (18.41)
Median change (Range)	-3.0 (-71;49)	-14.0 (-75;27)	-19.0 (-92;47)	-18.0 (-79;68)	-21.0 (-77;44)	-20.0 (-84;25)
P-value (vs. Placebo) [c,d]		<0.001	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-11.1 (2.27)	-11.0 (1.70)	-11.8 (1.65)	-14.5 (1.69)	-16.6 (2.34)
95% CI		(-15.61;-6.68)	(-14.31;-7.63)	(-15.00;-8.54)	(-17.82;-11.18)	(-21.23;-12.06)

[a] Based on ANCOVA model with treatment (placebo and ER OROS paliperidone arms in each protocol) and analysis center as factors, and baseline value as a covariate.
[b] Pairwise comparison: p-values associated with Dunnett's procedure.
[c] Based on ANCOVA model with protocol, treatment (placebo, ER OROS PAL 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) and analysis center within protocol as factors, and baseline value as a covariate.
[d] Comparisons with placebo without multiplicity adjustment.
Note: Negative change in score indicates improvement.
Cross-reference: Mod5.3.5.1\R076477-SCH-303\Table 15, Mod5.3.5.1\R076477-SCH-304\Table 15, and Mod5.3.5.1\R076477-SCH-305\Table 15.

Subgroup Analyses of Pooled Phase III trials (303, 304 and 305)

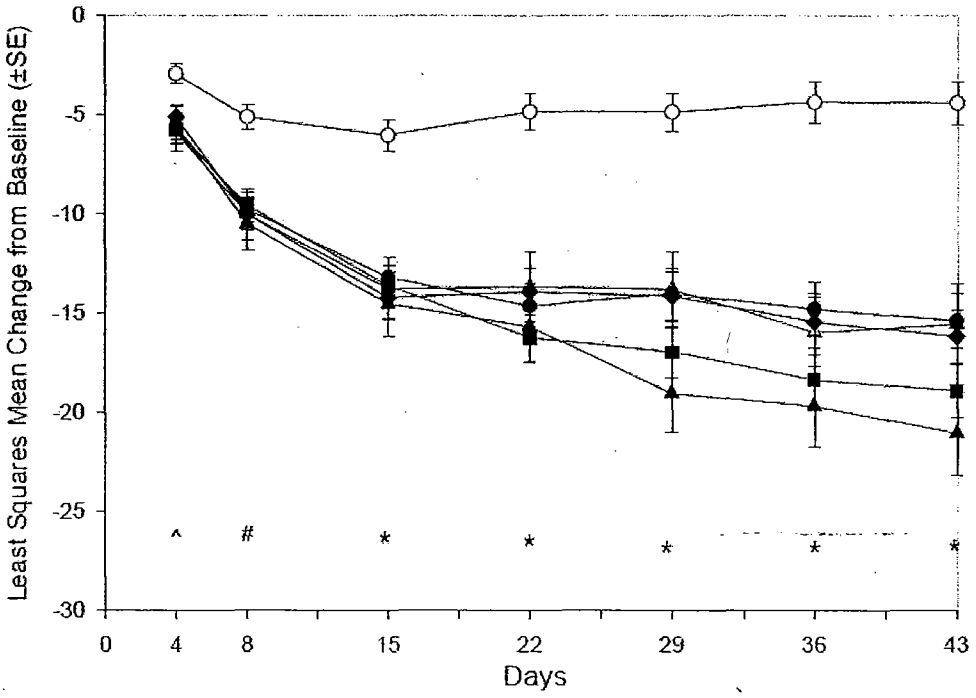
The sponsor examined efficacy results for 3 age-subgroups (18-25, 26-50 and over 50 year old age subgroups). These age-groupings were chosen in an effort to differentiate early onset schizophrenia (18-25 year olds) from late onset or chronic schizophrenia (over 50 year olds).

Reviewer Comment on Efficacy by Dose-level

Refer to previous Figures of each pivotal trial of the OC dataset results over time. These figures show little treatment group differences among Pal groups. The sponsor conducted a dose-level by effect analyses of pooled data of the LOCF dataset that suggests a dose-dependent effect on the primary efficacy variable. Similar analyses of the OC dataset could not be found in the submission. Yet upon visual examination of the above figures of the OC dataset clear or consistent differences among Pal dose-levels within any given study is not observable, even when comparing the lowest dose-level to the highest dose level.

The following shows results of pooled data using the LOCF dataset, as found in the submission which is more difficult to interpret.

Figure 2: Onset of Effect: Changes From Baseline in LS Means (±SE) for PANSS Total Score – LOCF: Pooled Data
(Studies R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305: Intent-to-Treat Analysis Set)



	N	Baseline Mean Total Score
Placebo	351	93.9
Paliperidone 3 mg	123	91.6
Paliperidone 6 mg	233	93.4
Paliperidone 9 mg	245	93.6
Paliperidone 12 mg	240	94.4
Paliperidone 15 mg	112	92.4

Comparisons of paliperidone vs placebo based on an Analysis of Covariance (ANCOVA) model with treatment, protocol, and analysis center as factors and baseline score as covariate.

^: 3 mg, 6 mg, 9 mg and 12 mg: All nominal p-values <= 0.05. Maximum was 0.021 (3 mg vs placebo). The observed nominal p-value was 0.071 between 15 mg and placebo.

*: **All Doses:** All nominal p-values <= 0.001.

#: **All Doses:** All nominal p-values <= 0.01. Maximum is 0.003 (3 mg vs placebo).

While efficacy between placebo and each Pal group is consistent when looking at either the OC or LOCF dataset consistent or clear differences between the Pal groups is not revealed for the OC dataset and LOCF datasets. Unlike the OC dataset, examination of the LOCF dataset shows some possible separation across treatment groups at the more extreme ends of the dose range. At least trends for greater effect may be observed when comparing the highest daily dose levels (e.g. the 15 mg or 12 mg dose-levels) to the lowest daily dose-level (3 mg). But this is only observed with the LOCF dataset and not with the OC dataset. When interpreting these results it is important to note that the OC dataset shows efficacy obtained over real time and across dose levels for only subjects who remain on the drug while the LOCF dataset does not show efficacy over real time but rather shows efficacy up to the time-point when subjects either dropped out early combined with subjects that completed the study. Therefore, the results of the LOCF dataset do not actually reflect effects over real time and do not show reflect results in the subjects that remain on the drug (which is clinically relevant information). Yet the LOCF dataset shows effects in as observed in a larger sample size early in treatment before subjects drop out due to lack of efficacy or for other reasons. A problem with pooling data is that it is difficult to interpret results across independent studies regarding an examination of dose-dependent effects and in turn with data from independent trials, pooled. Not all studies examined the same dose-levels. Such that the effect size in one dose-level in one study compared to a different dose-level used in another study is difficult to interpret. If this NDA is ultimately approved at the Agency level, then it is recommended that a figure of each study (by dose-level across time on the mean change on the PANSS total score) be provided and described in labeling for the OC dataset and results of the LOCF data set be described in which the primary endpoint be referred to as the mean change from baseline to treatment endpoint for subjects who stopped treatment early combined with subjects who completed treatment (in which the value of the last efficacy assessment was carried forward). It is recommended that the terms LOCF and OC be clearly defined in labeling. See the final section of this review for recommendations.

Reviewer Comment on Age Subgroup Analyses. *At least a greater numerical improvement on the primary efficacy variable was generally observed in Pal groups compared to the placebo group within each age-subgroup. However, one cannot assume that the over 50 year old age-group represent new onset (late onset) schizophrenia. Furthermore, subgroupings resulted in small sample sizes for the younger and older age-groups such that interpretation of results is difficult.*

Gender subgroups were also analyzed for efficacy in male and female subgroups.

Reviewer Comment on Gender Subgroup Analyses. *Each gender subgroup generally showed significantly greater or numerically greater efficacy in each Pal groups compared to the placebo group ($p<0.001$ without correcting for multiple comparisons).*

Geographical region sub-groupings were analyzed for efficacy.

Reviewer Comment on Efficacy Results for Geographical Region Subgroups *At least a greater numerical improvement on the primary efficacy variable was generally observed for each Pal group compared to placebo groups within each geographical-subgroup. However, several geographical region subgroups had small sample sizes such that results are difficult to interpret for at least these smaller subgroups.*

Geographical region sub-groupings were analyzed for efficacy.

Reviewer Comment on Efficacy Results for Subgroupings based on Race or Ethnicity *At least a greater numerical improvement on the primary efficacy variable was generally observed for each Pal group compared to placebo groups within each subgroup. However, many subgroups had small sample sizes such that results are difficult to interpret for at least these smaller subgroups.*

0Results of the above subgroup analyses are shown below (copied from the submission).

Table 28: PANSS Total Score- Change From Baseline to End Point by Age-LOCF: Pooled Data (Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
Age Group: 18-25	(N=45)	(N=24)	(N=27)	(N=41)	(N=35)	(N=17)
Baseline (N)	45	24	27	41	35	17
Mean (SD)	94.1 (12.22)	96.5 (11.81)	95.8 (9.48)	94.1 (12.58)	96.7 (11.55)	93.4 (16.44)
Median (Range)	94.0 (71;120)	95.5 (72;119)	95.0 (80;117)	92.0 (72;136)	98.0 (72;120)	88.0 (71;117)
End Point (N)	45	24	27	41	35	17
Mean (SD)	90.2 (28.15)	80.1 (21.12)	80.0 (20.90)	73.6 (19.88)	79.4 (25.51)	70.1 (20.81)
Median (Range)	93.0 (38;164)	80.0 (30;117)	77.0 (37;122)	71.0 (34;122)	74.0 (39;157)	68.0 (33;100)
Baseline Change (N)	45	24	27	41	35	17
Mean (SD)	-4.0 (24.46)	-16.4 (16.33)	-15.8 (19.72)	-20.4 (22.81)	-17.3 (23.16)	-23.2 (21.29)
Median (Range)	-6.0 (-71;44)	-14.5 (-59;10)	-17.0 (-80;15)	-22.0 (-73;35)	-16.0 (-55;44)	-17.0 (-84;6)
P-value (vs. Placebo) [a,b]		0.278	0.021	0.019	0.007	0.046
Diff. of LS Means (SE)		-7.0 (6.40)	-14.6 (6.24)	-12.6 (5.31)	-17.3 (6.28)	-14.4 (7.13)
95% CI		(-19.66;5.70)	(-27.02;-2.27)	(-23.17;-2.12)	(-29.76;-4.83)	(-28.55;-0.26)
Age Group: 26-50	(N=253)	(N=84)	(N=173)	(N=174)	(N=173)	(N=84)
Baseline (N)	253	84	172	174	173	83
Mean (SD)	94.0 (11.82)	89.8 (12.18)	93.7 (11.56)	93.5 (12.89)	94.4 (11.46)	91.9 (11.61)
Median (Range)	94.0 (70;120)	89.0 (71;123)	93.0 (70;123)	93.0 (67;131)	94.0 (70;121)	90.0 (65;118)
End Point (N)	253	84	172	174	173	83
Mean (SD)	89.2 (24.21)	74.2 (20.55)	76.6 (21.85)	78.4 (23.25)	72.5 (20.08)	73.6 (18.61)
Median (Range)	91.0 (30;164)	74.0 (30;125)	75.5 (30;138)	77.0 (30;176)	70.0 (31;129)	73.0 (30;121)
Baseline Change (N)	253	84	172	174	173	83
Mean (SD)	-4.8 (21.66)	-15.6 (21.01)	-17.1 (21.83)	-15.1 (20.62)	-21.9 (20.06)	-18.4 (17.44)
Median (Range)	-3.0 (-71;49)	-14.5 (-75;27)	-19.5 (-92;47)	-17.0 (-79;68)	-22.0 (-77;37)	-19.0 (-72;25)
P-value (vs. Placebo) [a,b]		<0.001	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-11.8 (2.82)	-11.4 (2.04)	-10.7 (2.00)	-16.3 (2.04)	-15.3 (2.82)
95% CI		(-17.35;-6.26)	(-15.44;-7.43)	(-14.63;-6.79)	(-20.26;-12.25)	(-20.88;-9.81)
Age Group: >50	(N=53)	(N=15)	(N=34)	(N=30)	(N=32)	(N=12)
Baseline (N)	53	15	34	30	32	12
Mean (SD)	93.1 (10.70)	93.8 (10.89)	89.6 (10.12)	93.5 (10.69)	91.6 (8.44)	94.0 (11.73)
Median (Range)	91.0 (72;118)	95.0 (77;113)	87.5 (73;117)	93.0 (73;113)	92.0 (78;120)	92.0 (79;120)
End Point (N)	53	15	34	30	32	12
Mean (SD)	87.4 (23.56)	84.7 (22.63)	73.3 (16.54)	72.1 (17.82)	74.1 (15.33)	68.3 (21.02)
Median (Range)	86.0 (41;139)	83.0 (48;140)	70.0 (47;107)	70.5 (30;108)	72.5 (32;103)	65.0 (42;103)
Baseline Change (N)	53	15	34	30	32	12
Mean (SD)	-5.7 (21.47)	-9.1 (15.93)	-16.4 (15.37)	-21.4 (19.92)	-17.4 (16.68)	-25.8 (20.58)
Median (Range)	-4.0 (-68;35)	-11.0 (-32;27)	-19.5 (-40;25)	-19.5 (-75;19)	-17.0 (-60;11)	-28.5 (-59;12)
P-value (vs. Placebo) [a,b]		0.891	0.037	0.275	0.178	0.091
Diff. of LS Means (SE)		-1.3 (9.64)	-10.8 (5.10)	-6.8 (6.19)	-7.3 (5.36)	-16.1 (9.42)
95% CI		(-20.50;17.84)	(-20.94;-0.67)	(-19.11;5.50)	(-17.93;3.38)	(-34.84;2.62)

[a] Based on ANCOVA model with protocol, treatment (placebo, ER OROS PAL 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) and analysis center within protocol as factors, and baseline value as a covariate.
[b] Comparisons with placebo without multiplicity adjustment.
Note: Negative change in score indicates improvement.

Table 37: PANSS Total Score - Change From Baseline to End Point by Geographic Region-LOCF: Pooled Data (R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
North America	(N=147)	(N=40)	(N=111)	(N=45)	(N=111)	(N=37)
Baseline (N)	147	40	110	45	111	36
Mean (SD)	94.2 (12.31)	95.1 (12.94)	92.3 (11.96)	96.1 (13.23)	94.1 (11.42)	94.8 (12.15)
Median (Range)	95.0 (70;120)	93.5 (74;123)	91.0 (70;119)	94.0 (72;131)	94.0 (70;120)	96.5 (70;113)
End Point (N)	147	40	110	45	111	36
Mean (SD)	87.5 (23.59)	77.7 (22.81)	76.6 (20.15)	85.8 (23.95)	76.5 (20.21)	80.7 (18.60)
Median (Range)	89.0 (33;139)	76.5 (37;125)	75.0 (33;138)	85.0 (36;176)	75.0 (40;157)	82.5 (44;109)
Baseline Change (N)	147	40	110	45	111	36
Mean (SD)	-6.7 (20.58)	-17.5 (23.23)	-15.7 (18.89)	-10.3 (24.94)	-17.5 (19.83)	-14.2 (16.19)
Median (Range)	-4.0 (-71;35)	-15.5 (-75;21)	-17.0 (-80;30)	-7.0 (-79;54)	-18.0 (-65;44)	-15.0 (-59;12)
P-value (vs. Placebo) [a,b]		0.004	0.004	0.224	<0.001	0.014
Diff. of LS Means (SE)		-11.7 (3.99)	-7.0 (2.44)	-4.7 (3.87)	-8.5 (2.43)	-10.1 (4.08)
95% CI		(-19.50;-3.83)	(-11.80;-2.21)	(-12.30;2.89)	(-13.32;-3.76)	(-18.14;-2.08)
Western Europe	(N=33)	(N=21)	(N=15)	(N=34)	(N=17)	(N=17)
Baseline (N)	33	21	15	34	17	17
Mean (SD)	93.7 (13.86)	93.0 (12.49)	93.5 (13.02)	93.1 (16.42)	92.4 (11.86)	94.6 (14.62)
Median (Range)	93.0 (71;120)	92.0 (72;113)	93.0 (73;117)	89.5 (70;136)	92.0 (74;109)	88.0 (74;120)
End Point (N)	33	21	15	34	17	17
Mean (SD)	81.7 (27.35)	77.7 (27.75)	79.3 (24.67)	72.9 (21.11)	69.8 (22.08)	61.7 (20.26)
Median (Range)	83.0 (30;164)	78.0 (30;140)	73.0 (43;127)	70.0 (34;117)	66.0 (32;118)	61.0 (30;93)
Baseline Change (N)	33	21	15	34	17	17
Mean (SD)	-12.0 (24.49)	-15.2 (23.81)	-14.1 (16.52)	-20.1 (19.64)	-22.5 (24.40)	-32.9 (22.71)
Median (Range)	-12.0 (-71;44)	-14.0 (-70;27)	-20.0 (-36;18)	-17.0 (-73;22)	-22.0 (-62;33)	-25.0 (-84;5)
P-value (vs. Placebo) [a,b]		0.994	0.229	0.095	0.023	0.010
Diff. of LS Means (SE)		0.0 (5.90)	-8.3 (6.86)	-8.2 (4.86)	-15.3 (6.62)	-16.5 (6.27)
95% CI		(-11.64;11.73)	(-21.88;5.29)	(-17.83;1.44)	(-28.38;-2.15)	(-28.92;-4.09)
Eastern Europe	(N=126)	(N=33)	(N=91)	(N=122)	(N=94)	(N=31)
Baseline (N)	126	33	91	122	94	31
Mean (SD)	94.5 (10.28)	92.6 (9.08)	94.4 (10.27)	93.8 (10.97)	94.5 (10.87)	92.6 (11.13)
Median (Range)	93.5 (70;120)	93.0 (76;109)	94.0 (73;123)	93.0 (67;129)	94.0 (71;121)	90.0 (78;118)
End Point (N)	126	33	91	122	94	31
Mean (SD)	94.1 (25.19)	78.2 (14.69)	74.9 (22.10)	76.7 (20.71)	71.4 (20.55)	75.6 (16.81)
Median (Range)	95.0 (41;164)	78.0 (38;115)	70.0 (30;131)	74.5 (30;152)	70.5 (31;137)	71.0 (42;121)
Baseline Change (N)	126	33	91	122	94	31
Mean (SD)	-0.4 (22.35)	-14.4 (13.11)	-19.4 (23.81)	-17.2 (19.08)	-23.2 (19.32)	-16.9 (17.25)
Median (Range)	0.5 (-68;49)	-14.0 (-43;23)	-20.0 (-92;47)	-20.0 (-75;68)	-23.0 (-77;36)	-16.0 (-48;25)
P-value (vs. Placebo) [a,b]		<0.001	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-16.2 (4.46)	-18.1 (2.84)	-17.0 (2.53)	-22.0 (2.82)	-19.4 (4.54)
95% CI		(-24.97;-7.46)	(-23.69;-12.52)	(-21.99;-12.04)	(-27.55;-16.46)	(-28.31;-10.45)
Asia	(N=45)	(N=29)	(N=17)	(N=44)	(N=18)	(N=28)
Baseline (N)	45	29	17	44	18	28
Mean (SD)	91.2 (11.56)	84.5 (11.67)	94.8 (9.77)	90.6 (12.35)	97.1 (10.82)	87.6 (11.72)
Median (Range)	89.0 (72;117)	81.0 (71;106)	96.0 (79;112)	91.0 (68;117)	101.5 (77;111)	87.0 (65;109)
End Point (N)	45	29	17	44	18	28
Mean (SD)	85.4 (21.98)	72.5 (19.80)	82.0 (17.83)	71.0 (22.88)	72.4 (19.47)	64.9 (16.28)
Median (Range)	83.0 (34;124)	73.0 (34;113)	82.0 (55;122)	71.0 (32;122)	80.0 (32;102)	68.0 (32;90)
Baseline Change (N)	45	29	17	44	18	28
Mean (SD)	-5.8 (21.53)	-12.0 (17.43)	-12.8 (16.93)	-19.6 (21.98)	-24.7 (21.03)	-22.7 (15.77)
Median (Range)	-9.0 (-53;35)	-11.0 (-41;23)	-18.0 (-38;14)	-18.5 (-60;35)	-15.0 (-74;0)	-24.5 (-44;12)
P-value (vs. Placebo) [a,b]		0.022	0.614	<0.001	0.015	<0.001
Diff. of LS Means (SE)		-10.7 (4.63)	-2.8 (5.58)	-14.4 (3.82)	-13.5 (5.49)	-20.5 (4.64)
95% CI		(-19.88;-1.57)	(-13.83;8.20)	(-21.94;-6.84)	(-24.38;-2.69)	(-29.63;-11.30)

[a] Based on ANCOVA model with protocol, treatment (Placebo, ER OROS PAL 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) and analysis center within protocol as factors, and baseline value as a covariate.
[b] Comparisons with placebo without multiplicity adjustment.
Note: Negative change in score indicates improvement.

Table 31: PANSS Total Score- Change From Baseline to End Point by Sex-LOCF: Pooled Data (Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
Sex: Male	(N=231)	(N=78)	(N=137)	(N=151)	(N=146)	(N=73)
Baseline (N)	231	78	136	151	146	72
Mean (SD)	94.3 (12.09)	90.5 (11.63)	92.6 (10.99)	93.7 (12.43)	92.9 (11.38)	93.1 (12.91)
Median (Range)	93.0 (70;120)	90.5 (71;123)	92.0 (70;119)	93.0 (67;136)	94.0 (70;120)	94.0 (70;120)
End Point (N)	231	78	136	151	146	72
Mean (SD)	89.7 (25.44)	75.3 (20.55)	78.3 (20.98)	77.8 (24.04)	74.9 (20.58)	72.2 (19.46)
Median (Range)	91.0 (31;164)	75.0 (30;140)	77.0 (33;131)	77.0 (30;176)	71.5 (31;137)	72.5 (30;121)
Baseline Change (N)	231	78	136	151	146	72
Mean (SD)	-4.6 (21.82)	-15.2 (18.68)	-14.3 (18.64)	-16.0 (22.34)	-17.9 (19.85)	-20.9 (19.58)
Median (Range)	-3.0 (-71;49)	-14.0 (-75;27)	-16.0 (-61;30)	-17.0 (-79;68)	-19.0 (-77;37)	-20.0 (-84;25)
P-value (vs. Placebo)[a,b]		<0.001	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-11.0 (2.93)	-9.5 (2.26)	-10.3 (2.15)	-12.6 (2.21)	-16.3 (2.98)
95% CI		(-16.80;-5.28)	(-13.91;-5.03)	(-14.55;-6.12)	(-16.95;-8.28)	(-22.19;-10.49)
Sex: Female	(N=120)	(N=45)	(N=97)	(N=94)	(N=94)	(N=40)
Baseline (N)	120	45	97	94	94	40
Mean (SD)	93.2 (10.86)	93.5 (13.02)	94.4 (11.52)	93.3 (12.80)	96.7 (10.46)	91.1 (11.33)
Median (Range)	94.0 (70;119)	94.0 (71;119)	94.0 (72;123)	93.5 (70;125)	95.0 (72;121)	89.5 (65;118)
End Point (N)	120	45	97	94	94	40
Mean (SD)	88.0 (22.94)	78.9 (22.03)	74.0 (20.98)	75.3 (18.84)	71.9 (20.27)	73.0 (18.74)
Median (Range)	88.5 (30;156)	77.0 (37;125)	70.0 (30;138)	74.0 (32;121)	70.5 (32;157)	70.5 (33;108)
Baseline Change (N)	120	45	97	94	94	40
Mean (SD)	-5.2 (22.28)	-14.6 (21.34)	-20.4 (22.93)	-18.0 (18.69)	-24.8 (20.01)	-18.1 (16.19)
Median (Range)	-2.0 (-54;46)	-15.0 (-69;27)	-22.0 (-92;47)	-19.5 (-64;35)	-23.5 (-70;44)	-19.5 (-45;22)
P-value (vs. Placebo)[a,b]		0.004	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-11.8 (4.12)	-12.9 (2.88)	-14.9 (2.85)	-16.5 (2.89)	-15.7 (4.27)
95% CI		(-19.89;-3.69)	(-18.60;-7.27)	(-20.54;-9.34)	(-22.16;-10.81)	(-24.08;-7.28)

[a] Based on ANCOVA model with protocol, treatment (placebo, ER OROS PAL 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) and analysis center within protocol as factors, and baseline value as a covariate.
[b] Comparisons with placebo without multiplicity adjustment.
Note: Negative change in score indicates improvement.

Table 34: PANSS Total Score- Change From Baseline to End Point by Race-LOCF: Pooled Data
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
Race: White	(N=217)	(N=61)	(N=152)	(N=170)	(N=156)	(N=50)
Baseline (N)	217	61	151	170	156	50
Mean (SD)	95.2 (11.59)	93.6 (10.41)	93.7 (10.45)	94.2 (11.62)	94.4 (10.89)	94.1 (11.84)
Median (Range)	95.0 (70;120)	94.0 (72;119)	93.0 (73;123)	93.0 (67;129)	94.0 (71;121)	93.5 (78;120)
End Point (N)	217	61	151	170	156	50
Mean (SD)	92.1 (25.11)	81.9 (20.56)	76.2 (21.88)	77.6 (20.23)	73.2 (20.53)	75.6 (17.81)
Median (Range)	94.0 (33;164)	78.0 (38;140)	72.0 (30;138)	76.5 (30;152)	71.0 (31;137)	72.5 (42;121)
Baseline Change (N)	217	61	151	170	156	50
Mean (SD)	-3.1 (22.39)	-11.7 (18.00)	-17.5 (21.54)	-16.6 (18.51)	-21.2 (20.30)	-18.5 (17.72)
Median (Range)	-1.0 (-71;49)	-11.0 (-69;27)	-20.0 (-92;47)	-19.0 (-75;68)	-22.0 (-77;37)	-18.0 (-55;25)
P-value (vs. Placebo)[a,b]		0.002	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-10.4 (3.25)	-14.3 (2.17)	-13.8 (2.05)	-18.3 (2.17)	-17.1 (3.45)
95% CI		(-16.75;-3.97)	(-18.52;-10.01)	(-17.78;-9.72)	(-22.54;-14.03)	(-23.83;-10.28)
Race: Black	(N=79)	(N=25)	(N=64)	(N=23)	(N=65)	(N=27)
Baseline (N)	79	25	64	22	65	26
Mean (SD)	91.7 (11.71)	92.6 (10.92)	92.2 (13.31)	94.4 (15.93)	93.7 (11.93)	94.8 (12.73)
Median (Range)	91.0 (70;117)	90.0 (74;119)	91.0 (70;117)	93.0 (72;136)	94.0 (70;120)	96.0 (70;117)
End Point (N)	79	25	64	22	65	26
Mean (SD)	83.1 (23.32)	72.6 (21.88)	75.9 (19.97)	82.5 (24.69)	75.6 (20.85)	75.1 (23.02)
Median (Range)	85.0 (30;132)	76.0 (30;117)	77.0 (33;113)	80.5 (34;117)	76.0 (43;157)	81.0 (30;109)
Baseline Change (N)	79	25	64	22	65	26
Mean (SD)	-8.6 (21.09)	-20.0 (20.62)	-16.3 (19.86)	-11.8 (28.78)	-18.1 (19.72)	-19.7 (23.71)
Median (Range)	-6.0 (-71;28)	-17.0 (-70;7)	-15.0 (-80;25)	-7.0 (-73;35)	-20.0 (-65;44)	-17.0 (-84;9)
P-value (vs. Placebo)[a,b]		0.545	0.096	0.818	0.055	0.318
Diff. of LS Means (SE)		-3.2 (5.31)	-5.8 (3.49)	1.3 (5.52)	-6.8 (3.51)	-5.3 (5.31)
95% CI		(-13.69;7.25)	(-12.71;1.04)	(-9.60;12.14)	(-13.67;0.16)	(-15.79;5.16)
Race: Asian	(N=28)	(N=30)		(N=28)		(N=29)
Baseline (N)	28	30		28		29
Mean (SD)	89.7 (11.80)	85.1 (11.86)		88.1 (12.13)		88.2 (11.90)
Median (Range)	88.5 (72;116)	82.0 (71;106)		86.5 (68;117)		87.0 (65;109)
End Point (N)	28	30		28		29
Mean (SD)	90.1 (23.86)	73.0 (19.64)		70.0 (22.73)		66.2 (17.48)
Median (Range)	89.5 (43;124)	73.0 (34;113)		68.5 (32;122)		69.0 (32;103)
Baseline Change (N)	28	30		28		29
Mean (SD)	0.4 (21.28)	-12.1 (17.13)		-18.1 (20.14)		-21.9 (16.00)
Median (Range)	-4.0 (-43;35)	-12.5 (-41;23)		-18.0 (-60;35)		-24.0 (-44;12)
P-value (vs. Placebo)[a,b]		0.014		<0.001		<0.001
Diff. of LS Means (SE)		-12.2 (4.88)		-17.7 (4.92)		-22.1 (4.87)
95% CI		(-21.94;-2.55)		(-27.41;-7.89)		(-31.76;-12.44)
Race: Other	(N=27)	(N=7)	(N=18)	(N=25)	(N=19)	(N=7)
Baseline (N)	27	7	18	25	19	7
Mean (SD)	93.9 (10.78)	98.6 (21.61)	94.6 (9.55)	95.0 (14.89)	96.3 (11.07)	88.6 (13.82)
Median (Range)	92.0 (75;117)	110.0 (73;123)	95.5 (79;112)	97.0 (71;131)	101.0 (77;111)	84.0 (71;109)
End Point (N)	27	7	18	25	19	7
Mean (SD)	80.9 (20.61)	60.7 (17.87)	81.0 (17.81)	74.0 (30.12)	71.7 (19.17)	66.3 (14.10)
Median (Range)	80.0 (34;119)	55.0 (42;86)	80.5 (55;122)	74.0 (38;176)	78.0 (32;102)	62.0 (53;93)
Baseline Change (N)	27	7	18	25	19	7
Mean (SD)	-13.0 (18.68)	-37.9 (24.35)	-13.6 (16.72)	-21.0 (29.05)	-24.6 (20.44)	-22.3 (11.32)
Median (Range)	-10.0 (-53;19)	-32.0 (-75;-12)	-21.0 (-38;14)	-18.0 (-79;54)	-16.0 (-74;0)	-18.0 (-44;-10)
P-value (vs. Placebo)[a,b]		0.009	0.923	0.097	0.080	0.231
Diff. of LS Means (SE)		-27.7 (10.28)	-0.6 (6.49)	-9.8 (5.86)	-11.6 (6.54)	-13.8 (11.46)
95% CI		(-48.13;-7.25)	(-13.53;12.27)	(-21.51;1.81)	(-24.60;1.40)	(-36.62;8.95)

[a] Based on ANCOVA model with protocol, treatment (placebo, ER OROS PAL 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) and analysis center within protocol as factors, and baseline value as a covariate.
[b] Comparisons with placebo without multiplicity adjustment.
Note: Negative change in score indicates improvement.

6.1.6 Clinical Microbiology

No information on "clinical microbiology" was provided.

6.1.7 Efficacy Conclusions

Reviewer Conclusions and comments: *The results of pivotal Phase III studies are positive for showing greater improvement on the primary efficacy variable in Pal groups compared to placebo groups. The elderly Study -302 shows at least trends for greater improvement. The elderly study was small such that failure to show significant group differences may be due to insufficient sample size. Due to the small sample size in this study, the results are difficult to interpret.*

The results shown in Table 39 did not show that results were corrected for multiple comparisons between each Pal dose-level and placebo subjects. However, at least numerical trends for greater efficacy in Pal groups at all dose-levels examined compared to placebo was observed. Therefore, a daily dose-level as low as 3 mg may be beneficial to at least, some patients. The final section of this review of this review provides for further comment regarding proposed treatment regimen and dose-levels for the proposed indication.

See previous reviewer comments in this Section addressing other potential issues relevant to efficacy findings.

Refer to Section 9 for reviewer conclusions, comments and recommendations relevant to efficacy for this NDA.

7 INTEGRATED REVIEW OF SAFETY

To aid the reader the following provides an overview of safety findings which is followed by more detailed reviewer comments and summary of each safety variable followed by the sponsor's data (some of the data could only be found in multipaginated tables with as many as 50 or more pages in some cases, such that only sections of these summary tables are displayed or results are summarized rather than being displayed).

Several Safety Signals Consistent with Known Drug Class Effects were Observed in Phase III Trials:

1. *Orthostatic hypotension and tachycardia associated with orthostatic hypotension.*
2. *Hyperprolactinemia*
3. *Subjects that developed hyperglycemia*
4. *Lipid profile effects*
5. *Weight gain*
6. *Somnolence*
7. *Extrapyramidal system effects*
8. *Neuroleptic Malignant Syndrome (NMS): one subject with NMS was reported although there may be at least one additional subject (subjects 100057, 200213)*

Suicidality (includes a few completed suicides) that is known to be inherent in the schizophrenia population but occurred with an incidence of 3% in the 15 mg Pal group compared to 0-1% in

lower dose Pal groups (except that the 3 mg group had an incidence of 2%) and placebo. It is not clear if this is a real dose dependent effect due to the following reasons:

- *Due to the relatively smaller sample size of the 15 mg group compared to most other treatment groups,*
- *Due to multiple between group comparisons,*
- *The between group difference between this group and placebo is small,*
- *The lowest dose group had an incidence of 2%, which is inconsistent with a real signal, since the 3, 6, 9 and 12 mg group had a lower incidence and is only 1% less than the incidence in the 15 mg group*
- *Among other considerations, such as those described in Section 7.2.8 of this reveiw discussing challenges and potential concerns with identifying and enumerating subjects with suicidality.*

Risperdal® labeling describes ADOs of suicide attempt in 1.2% of Risperidone treated subjects compared to 0.6% placebo subjects in their clinical trials for the schizophrenia indication (under Adverse Reactions). Risperdal® has a suicide subsection under Precautions (indicating the risk of suicide that is known to exist in this patient population and the need for close monitoring but only describes the ADOs of suicidality under the Adverse Reactions section).

One subject with Thrombotic Thrombocytopenic Purpura is described in a subsection in Risperdal® labeling under Precuations.

The following observations are noted:

- *Thrombocytopenia was reported as an SAE (100847) in a subject in Study -301 (a "prevention relapse trial). Decreased platelet count was first noted on Day 71 of Pal treatment (12 mg daily). The subject was given the diagnosis of pancytopenia (based on CBC) secondary to a nutritional deficiency. This subject recovered after Pal cessation and nutritional supplementation. In the absence of diagnostic tests (e.g a bone marrow biopsy and B12, folate levels) the role of Pal is unclear.*
- *Clinically unremarkable decreases in group mean values of HgB and platelet count were observed in Pal treatment groups (and not in placebo subjects) in Phase III trials (as described below).*
- *Platelet count appears to show greater decreases with 6-12 month continuous antipsychotic treatment (compared to shorter treatment durations), but the magnitude of these mean decreases is clinically unremarkable (observed in Phase III OL extension trials that is primarily based on updated results in the 120-Day SUR).*
- *Decreased platelet count with chronic treatment appears to be greatest in the group of OL Pal subjects (in the OL extension trials) that previously received DB Olanzapine treatment (in the DB Phase III lead-in studies). But the magnitude of the decrease was clinically unremarkable (primarily based on updated results in the 120-Day SUR).*
- *The most prominent signal for low platelet count was in a small elderly short-term Phase III trial showing an incidence of 8% and 3% in 3-12 mg flexible dose Pal group and placebo group, respectively. However, the sample size was quite small (approximately 30 or more placebo subjects and approximately 70 or more Pal subjects)*

Seizures in a few subjects (at least subjects 200986, 500108) are described in Section 7.1.3.3 I of this review. It is not clear if there are other subjects (e.g. there may be subjects with seizure but believed to have syncope for example, so that an accurate count is difficult to determine). Subjects with reported seizure or syncope are listed in SAE and ADO summary tables in this review and several subjects are described in Section 7.1.3.3. I, including one additional ***patient that had seizures prior to death*** *(subject [redacted] reported in a Safety Alert Report under the Pal OROS IND).*

Common AEs (5% in any group) in Phase III trials were generally similar for drugs in the drug class as described in Section 7.1.5 except for the incidence of 1°AV block which occurred in 4.4% at the highest dose-level (15 mg Pal) compared to 1.4% of placebo. See findings on PR prolongation below.

Potentially Unexpected Safety Signals Based on Safety Results of Phase III trials
Note that all mean changes discussed below are relative to baseline values unless otherwise specified.

Unexpected hemodynamic/cardiovascular or cardiac effects:
Dose-dependent QT prolongation effects *of Paliperidone. Such an effect is not described in Risperdal® labeling. However, there are other drugs in this drug-class with this effect.*

QTc group mean increases were observed in pal groups compared to placebo in the DB Phase III studies. These mean increases:

- *Did not appear to occur at all assessment time-points (primarily only observed on the days having more frequent post-dose assessments following daily administration).*
- *Appeared to occur near Tmax,*
- *Appeared to also be influenced by confounding variables (primarily based on results of Study SCH-1009 with supporting evidence from the Phase III trial results).*

The ***greatest group mean increases was a mean increase of 7.2 ±25 msec in QTraw*** *(median increase of 11.0 msec) at the 12 month assessment time-point in the subgroup with the longest continuous Pal exposure (in OL Phase III extension trials based on results in the 120-Day SUR in Section 7.2.9.1). Note the following:*

- *This subgroup was the group in the OL pal trials that was previously exposed to DB Pal in the 6-week lead-in Phase III trials that had over 6 months of continuous Pal treatment (DB and OL treatment).*
- *This subgroup also had the largest sample size at assessment time-points over the last 6-12 months of OL Pal treatment in the 1-year OL trials (as found in the 120-Day Safety Update Report).*

- *Since heart rate was not generally altered during chronic treatment (-2.9 to 0.1 bpm over the 6-12 months of treatment in this subgroup) these results (and those above) are based on QTraw mean changes.*
- *QTcLD mean change (which appears to be the sponsor's preferred method of correcting for QT values) was 3.2±14 msec at 12 months of OL Pal treatment in this subgroup.*
- *Other time-points during the last 6-12 months of OL pal treatment also showed group mean increases in QTraw and QTcLD interval in this group that were generally found to be numerically greater than values at earlier OL time-points.*

QT mean appeared to be influenced by Cmax, Tmax and by confounding variables (based on results of Phase III trials and Study –SCH-1009).

Results on the incidence of outliers on QTcLD (results on QTraw outliers or scatterplots could generally not be found) also suggest the following:

- *A greater effect over chronic treatment in which the above DB Pal/OL Pal treatment group showed an incidence of 11% of 30-60 msec QTcLD interval shifts in the over 6 month exposure subgroup compared to 5% in the ≤ 6 month exposure subgroup. These results are limited by the absence of placebo group (as are the results on mean and median changes) but could be reflecting a real signal and warrant further exploration.*
- *2.5% of DB-Pal/OL-Pal subjects had QTcLD values of 450 msec or greater in OL trials (in the 120-Day SUR) and 1.9% of all DB Pal subjects of DB Phase III trials met this outlier criterion in QTcLD (1.4% of Placebo subjects exceeded 450 msec in DB trials). Fewer subjects had QTcLD values of over 480 msec.*

None of the subjects had a QT or QTcLD value of 500 msec or greater in DB and OL Phase III trials.

Several Pal subjects had QTc prolongation reported that generally also had other hemodynamic or related events that were sometimes SAEs or ADOs that included non-elderly and elderly subjects.

- *2 ADOs due to QTc prolongation (QTcB over 450 msec) on day 4 were reported in Pal subjects of the elderly Phase III trial (subjects 200514 and 200119) in which one of these subjects also had QTcF of over 500 msec (QTcB is likely to be misleading yet it is not clear what QTcF was in the other subject).*
- *A 65 year old female (200614) was reported to hae QTcLF and QTcF of 450-454 msec on Day 5 after a daily dose increase of Pal from 6 to 9 mg who also had a "mild ventricular arrhythmia." This subject completed the study without sequelea.*

Time-dependent effects on increasing supine heart rate that occurred in the absence of concurrent orthostatic vital sign changes and clinically remarkable subjects with this event that could be reflecting the influence of confounding variables including PK proporties:

- *Refer to drug class labeling and Olanzapine labeling for descriptions of tachycardia with the focus on tachycardia associated with orthostatic hypotension under Precautions.*
- *A group mean increase of up to 6.8±13 bpm was observed in the 15 mg Pal group compared to almost no change in mean heart rate (at supine) in the placebo group (smaller mean increases were observed in lower dose Pal groups) or in the 10 mg/day Olanzapine group in the short-term Phase III trials.*
- *Pal effects on vital signs appears to be strongly influenced not only by Cmax levels, but also to confounding variables that are time-dependent, as suggested by safety results from the Phase III trials (see Section 7).*

*2 **food effect Single-Dose Phase I studies (using either 12 mg or 15 mg Pal Phase III or [redacted] formulations) employed more frequent vital sign assessments** over a longer post-dose time period than was employed in Phase III trials that **revealed:***

- ***Food effects on PK and in turn on mean increase in systolic BP (13.5 mmHg in the fed [redacted] 15 mg Pal treatment condition at 36 hours post-dose)** that began at approximately 29 or 30 hours post-dose that was less prominent in the fasted conditions in both Phase I studies (in one study subjects were released from bed rest at 30 hours post-dose but the other study had an ambulatory condition that also showed this food effect on increased BP).*
- ***Group mean increase in heart rate to a similar extent in fasted and fed treatment conditions** was also observed that occurred near the same time as the increased BP. Other vital sign changes were observed in these trials.*
- *Refer to Section 7.1.12 C for additional safety findings and Section 7.1.3.3. E for clinically remarkable subjects.*

SAEs and ADOs involving supine tachycardia (without orthostatic hypotension found in the narrative) associated with other related events, such as ECG changes, symptoms such as dyspnea and/or other vital sign changes that were strongly suspicious of Pal induced events given the timing and nature of the events and the baseline status of the subjects. Example of these events are as follows (see Section 7.1.3.3 for additional observations):

- *Subject 200973 (a 28 year old male taking 6 mg Pal/day) reported as an ADO with SAEs who had sinus tachycardia, non-specific ST wave changes with dyspnea and increased blood pressure, reported.*
- *Subject 500603 was an 18 year old (in the 9 mg Pal group) who was an ADO with SAEs of similar events to those of the previously described subject.*

A potential small (clinically remarkable) group mean increase in supine systolic BP (sBP)** also appeared to be observed **in the 15 mg Pal group (4±12.9 mmHg)** that was **not observed in lower dose Pal groups or in the placebo group in Phase III trials.
Some clinically remarkable Pal subjects had various hemodynamic changes that sometimes included increased blood pressure:

- *Subject 100201 had a history of hypertension that appeared to be well controlled by an antihypertensive agent prior to Pal treatment. This subject appeared to show an exacerbation of hypertension during Pal treatment (requiring the addition of*

antihypertensive drugs and increases in the dose) that led to an ADO (due to high blood pressure).

- *Subject 200601: a 30 year old male who developed a systolic blood pressure of approximately 170 mmHg during the first 7 days of Pal treatment when vital sign effects appear to be the greatest (he had a past history of hypertension but was not taking antihypertensives and appeared to have normal vital signs at baseline).*

Potentially greater vital sign changes in subjects receiving over 6 months of treatment compared to subjects receiving less than 6 moths of treatment in OL Pal Extension Trials, *as follows (based on the incidence of outliers for each of the following parameters, as found in the 120-Day SUR):*

- *Decreased supine systolic BP (4-5% incidence in > 6 month exposure subgroups compared to 0-1% incidence in ≤ 6 month exposure subgroups in the OL Pal long-term trials).*
- *Increased supine heart rate of generally over 10% in > 6 month exposure subgroups compared to 0-4% incidence in ≤ 6 month exposure subgroups,*
- *Increased standing systolic BP may also show this pattern but exposure subgroup differences were small.*

The above observations are limited by the absence of a placebo group. Also, subjects that are monitored longer and more frequently have a greater chance of meeting outlier criteria. Yet, the incidence of outliers in the opposite direction (e.g. for increased supine systolic BP, decreased supine heart rate) did not show this pattern for more outliers in the > 6 month exposure subgroup and the incidence was generally smaller than was observed in the above outlier categories. Consequently, the findings suggest a real effect over time.

Sinus pause, hypotension and bradycardia *were observed in Subject 300541 and sudden death in subject [redacted] (reported in a safety alert report under the IND for this drug). Approved labeling for olanzapine describes 3 normal volunteers in Phase I trials who had hypotension, bradycardia and sinus pauses following either oral olanzapine (in 1 case) or intramuscular olanzapine (in 2 cases).*

Episodes of hypotension and widely fluctuating BP occurred in a elderly subject *(200302)* ***who also developed NSST wave changes (first noted on Day 4)*** *who was hypertensive at baseline (the subjects was in the elderly Phase III trial receiving 9 mg Pal daily) who developed unstable angina and was an SAE and ADO due to "acute coronary syndrome." While this subject was likely to have pre-existing coronary disease the timing and nature of the vital sign related events are suspicious of being Pal related (at least partly related). Note the greater incidence of AEs of hypotension and AEs of hypertension in the elderly Phase III study, as shown below which was greater in Pal compared to placebo subjects.*

PR prolongation *was observed in Phase III trials but was not clinically remarkable in the magnitude of this effect. The largest group mean increase (from baseline) was 4.3 msec was at the highest dose-level (in the 15 mg Pal group) on Day 8 of DB treatment compared to -0.1 to 1.7 mean change at previous time-points and compared 0.5 to -1.9 mean changes in the placebo group during the DB phase in short-term Phase III trials. The 15 mg group was the only one to*

have a dose increase which occurred on Day 8 (from 12 mg daily to 15 mg daily). Therefore, these observations could be reflecting an effect of increasing the dose, in additional to an effect of dose-level. This drug effect is a noteworthy finding given the following related observations, suggesting a similar drug effect in other subjects and studies:

- ***Events in subject 300541 (12 mg Pal group)** described below of **hypotension, bradycardia (38 and 40 bpm at standing and supine), dizziness and possibly syncope, and multiple "pauses" of up to 8 seconds** found by holter monitoring) that also appeared to have an underlying cardiac disease (detected by ECG findings).*
- *1° AV-Block reported in 4.4% of 15 mg pal subjects compared to 1.4% placebo subjects in the short-term Phase III trial dataset,*
- *3% of Pal (2/76 subjects) and 0% of Placebo (0/38 subjects) in the small elderly Phase III study -302 (using flexible dose design of 3-12 mg daily).*

***Small, clinically unremarkable Pal group mean decreases in platelet count, hemoglobin, and reticulocyte count** (see above item 10 for an outline of results on decreased platelet and Section 7.1.7 of this review). The large variance (e.g. between subject and within subject over time) on platelet count can potentially be a limitation in detecting a potential drug effect in the clinical trials (as is the case with CPK levels described below).*

Clinically Remarkable Subjects with Elevations in LFTs (and in some cases elevations of CPK also occurred that were sometimes associated with elevations in GGT).

***Inconsistent Elevations of CPK were observed in Phase III trials** (across treatment groups, sometimes also observed in the placebo group, with dramatic fluctuations over time within a given subject). This observation could be due to non-drug-related reasons, since elevated CPK is not uncommon in the schizophrenia population, as the sponsor concludes (e.g. acute patients can be highly agitated, hyperactive, be receiving multiple IM injections, among other potential factors). The sponsor also concludes that individual elevations in CPK were generally not due to AEs (e.g. extrapyramidal symptoms). However, results of data analyses to support this conclusion could not be found in the SCS of the submission or in CSRs. Furthermore, when baseline values vary across subjects, groups and over time (as observed in the Phase III trials) it can be difficult to detect a potential drug effect on the given parameter. Morever, **Phase I trials of healthy subjects (who were not psychiatric patients) also revealed a greater group mean increase in CPK in high-dose OROS pal subjects (9 to 15 mg) than in the low dose OROS Pal subjects (3 to 6 mg).** Also CPK elevations were sometimes observed in subjects of Phase III and possibly Phase I trials with elevations with LFT in which other etiologies of CPK elevations could not be found in the narrative, as described, below. Elevations were also observed in the OL Phase III trials after chronic treatment. It would appear that a patient population (e.g. indirect) effect on CPK would no longer account for CPK elevations after long-term treatment in a more stable population. Consequently, CPK results are difficult to interpret and require further explanation. A response to an inquiry about the findings in Phase I trials was recently received, late in the review cycle, such that the submission (N005) has not been fully reviewed at the time of this writing.*

The following incidence of AEs in the elderly Phase III trial (Study -302) that are notable (a 6-week, flexible dose, parallel group study using 3-13 mg/day of Pal compared to a placebo group):

- *Incidence of sinus tachycardia and tachycardia AEs were 0% in placebo (for each AE) compared to 5% of each AE in the Pal group.*
- *QT prolongation was reported in 7% of Pal subjects compared to 3% of placebo subjects.*
- *The following were observed in the elderly trial but not the sort-term Phase III trials that were primarily of non-elderly patients (the incidence of Pal and placebo groups are shown):*
    - *Hypertension (5%, 3%, respectively)*
    - *Hypotension (5%, 0%): one cannot assume that hypotension in these subjects was orthostatic hypotension.*
    - *1° AV block in 3% (2 out of 76 Pal subjects) compared to 0 placebo subjects (out of 38 subjects).*

Some additional potentially clinically remarkable subjects are described in Section 7.1.3.3 (subjections C and I) of this review. There is also a subsection on syncope describing additional subjects with syncope not described above.

Potential Formulation (OROS) Related Adverse Events
The sponsor does not report any events related to gastrointestinal obstruction with respect to potential OROS formulation-related AEs. However, the undersigned reviewer found one subject with duodenal rupture (subject 201333) and another with gastrointestinal hemorrhage (subject 501122) described in Section 7.1.3.3.Q of this review that had this event reported on Day 37 (in the 6 mg Pal group of one of the short-term Phase III trials) who required surgery. A past medical history or concomitant medications to explain this event could not be found in the narrative. Therefore, the role of the OROS formulation is suspected (in the absence of alternative explanations or clear risk factors in this subject).

7.1 Methods and Findings

The safety data from clinical trials is outlined below (trials are summarized in Section 4.2 of this review) which provided the safety results described in Section 7 of this review.

Safety results from the N000 submission are described in Section 7.1 of this review, while safety results provided in the Safety Update Report (SUR) are described in Section 7.2.9 of this review in accordance with the Clinical Review MAPP.

In summary, the majority of safety data in the N000 submission that is relevant to the sponsor's proposed indication and recommended daily dose-range (3-12 mg with a starting daily dose of 6 mg) as described in proposed labeling is the following. Safety data came from three 6-week Phase III Trials (Studies -303, -304 and -305 of almost entirely non-elderly subjects) provided the bulk of integrated safety over short-term 6-week exposure of Pal treatment in these placebo

controlled, DB trials. A small 6-week Phase III Trial of elderly subjects (-302) provided unpooled data (placebo controlled, DB study). Limited longterm safety data came from ongoing open-label (OL) trials (-702, -703, -704, -705) of which the data was pooled. Most subjects in these trials had 6 months or less of exposure. These results are described in Section 7.1 of this review.

The 120-Day SUR provided the majority of longterm safety data (integrated) that included up to 1 year of OL Pal exposure that waswithin the ICH guidelines. These results came from primarily the ongoing OL extension trials (-702, -703, -704, and -705, pooled data). Section 7.2.9 of this review provides the results from this pooled dataset.

Safety Data Provided in the Original N000 Submission

I. Short Term Phase III Safety Data:

Pooled data from 3 Pivotal 6-week Phase III Trials (Studies -303, -304, -305): the safety data from these DB, placebo controlled, fixed dose, trials of primarily non-elderly schizophrenia patients were pooled given the similarity in study design and study population. The daily dose-levels of Paliperidone that was examined in a parallel group design for each study were as follow: 6, 9 and 12 mg/day in Study -303, 6 and 12 mg/day in Study -304, and 3, 9 and 15 mg/day in Study -305 and each study had an active control group: 10 mg/day of Olanzapine.

See Section 4 and Section 6 for a summary of the study design in these trials. Note that the 15 mg group was started on 12 mg daily for one week before receiving 15 mg daily which was given for the remainder of the DB phase. Dosing was to occur in the morning. Subjects were not monitored with respect to timing or content of meals.

Data from 1 elderly Phase III schizophrenia, flexible dose (3-12 mg daily), 6-week, placebo controlled trial (Study -302): safety data from this study were analyzed as an individual study (unpooled).

Reviewer Comment: *The main focus of the review was on the completed Phase III trials and the integrated longterm safety dataset provided from Phase III OL extension trials (below).*

II. Limited and Blinded Safety Data from an Ongoing Phase III "prevention of recurrence" Trail (Study -301) and the Open-Label Extension Trial (Study -701)

Limited Blinded Data (only listings of deaths and SAEs) from 1 Ongoing Phase III "prevention of recurrence" trial (Study -301): this study has an 8-week OL-run-in phase, then a 6-week OL stabilization phase, followed by a placebo controlled, DB treatment phase (1:1 of placebo or Paliperidone treatment). Treatment was flexible during the OL run-in and DB treatment phases (3 to 15 mg daily) but was fixed during the OL stabilization phase (at the dose identified during the stabilization phase).

Since this study is ongoing and has a DB phase in which study drug remains blinded, a Clinical Study Report (CSR) was not provided in the submission and only listings of deaths and SAEs (but not ADOs) are provided (as of 8/31/05) in which only COMIS forms, instead of narratives are provided for reported SAEs between cut-off dates of 5/31/05 and 8/31/05.

As described below, this study was completed in time for safety data to be included in the Safety Update Report submission.

Limited and unpooled data is provided for an Ongoing Study -701, an OL Extension Trial to the "Prevention of Recurrence" Study -301. Study -301 was completed in time for safety data from this trial and from -701 to be included in Safety Update Report submission (as described below).

The sponsor was asked to clarify the rationale for the breakdown (subcategorization) of dose groups into "low" versus "high" dose groups and the following was their response (copied from their N001, 1/10/06 response submission):

> "While all the safety data is important, the lowest doses tested (ER OROS paliperidone ≤6 mg) were believed to provide more relevant safety information for the population of interest in the submission (patients with schizophrenia) than the higher doses, thus both groups were included, but a distinction was made between the two. The terms "low" and "high" have been selected to differentiate the lowest doses of the ER OROS paliperidone from the higher doses and should not be considered a reflection of their perceived clinical benefit."

III. Longterm Safety Data in 6-12 Month Open-Label Extension Trials in Which Most Subjects had 6 Months or Less Pal Exposure

Pooled data from 4 Ongoing Phase III OL Extension Studies -702, -703, -704, -705

Since these studies are ongoing CSRs are not provided. Safety results on clinical parameters and incidence of AEs (using data from the last assessment on or before the May 31, 2005 cut-off date) is provided for 2 subgroup of subjects, categorized on the basis of total duration of Pal treatment (includes duration of exposure in the given 6-week DB lead-in study combined with OL exposure during the given OL Extension trial):

- ≤ 3 month exposure subgroup and
- > 3 month exposure subgroup

Since the studies are ongoing CSRs are not provided.

See section 4 of this review for a summary of the trial design and treatment.

See Table series 10.6 in the appendix of this review for a more information on how dose-groups were pooled by the sponsor.

Reviewer Comment. *Clarification on methods for categorizing subjects into low and high dose groups (as above) and the rationale for this breakdown was provided upon request in a 1/11/06 N001 submission (see methods in Table series 10.6) and the following rationale was provided:*

> "Healthy volunteers are known to tolerate this class of drugs less well than patients with schizophrenia. While all the safety data is important, the lowest doses tested (ER OROS paliperidone ≤6 mg) were believed to provide more relevant safety information for the population of interest in the submission (patients with schizophrenia) than the higher doses, thus both groups were included, but a distinction was made between the two."

Results supporting the above conclusion could not be found the sponsor's response submission. It is generally believed that healthy volunteers are more vulnerable to some effects of the drug (e.g. risk for dystonic reactions), it is not clear to the undersigned reviewer that this applies to all adverse drug effects (e.g. QT prolongation). Furthermore, the schizophrenia population has greater morbidity and is reported to be at greater risk of mortality than the general population. Consequently, the risk for some adverse drug effects (e.g. weight gain, lipid profile effects, cardiovascular effects) or secondary effects (clinically remarkable complications secondary to primary drug effects such as a potential complication of ischemia or risk for ischemia, for example) could be greater in the schizophrenia population than in the generally population.

Pooled from 3 Phase I/IIa trials of schizophrenia patients. See Section 4 of this review for a description of these 3 Trials. These studies included at least 100 Pal treated subjects.

Unpooled data from 7 "Other Phase I/IIa trials." These studies were not pooled due to unique study designs that were employed, such as a special study population PK trials (e.g. patients with renal impairment), or examining drug-drug interactions, or a study designed to yield "supratherapeutic plasma levels" to examine cardiovascular safety in patients with schizophrenia or schizoaffective disorders (Study –SCH-1009). Since study -1009 was a focused clinical safety study Study –1009 the results of this study are summarized under subsection 7.1.12 of this review.

IV. 1-Year Longterm Safety Information for Phase III OL Pal Trials Provided in 120-Day Safety Update Report

Refer to a separate section of this review for a description of safety datasets in the 120-Day Safety Update Report, in accordance with the clinical review MAPP (Section 7.2.9). The majority of safety data reviewed in this

V. Narratives and CRFs in the N000 and in the 3/29/06 120-Day Safety Update Report Submissions:

The sponsor reports deaths, SAEs and ADOs using two cut-off dates, 5/31/2005 and 8/31/2005. Narratives and CRFs are provided for deaths (SAEs and ADOs) occurring by the former cut-off date, while Safety reports (CIOMS forms) are provided for deaths (SAEs and ADOs) that occurred from 6/10/05 through 8/31/05. CRFs are provided for each narrative of deaths, ADOs and SAEs of the completed Phase I-III trials and for ongoing OL extension trials (-702 through -705). Narratives and CRFs were provided for Studies -301 and OL extension trials, -701-705 studies in the 120-Day SUR.

The majority of the longterm safety data (exposures of up to 6 and 12 months within ICH guidelines) was provided in the 120-Day Safety Update Report Submission (SUR, letter date 3/29/06) provided the narratives and CRFs of deaths, SAEs and ADOs for the more recently "Prevention of Recurrence" trial, Study -301 and for open-label trials (Studies -701-705) using the cur-off date of 11/1/05 (narratives or narrative summary tables generally included hyperlinks to the CRFs). Safety (CIOMS) reports were provided for SAEs and ADOs at the cut-off-dates of 11/2/05-12/31/05.

VI. Other datasets or datasources:

Section 7 also provides safety information from the literature and postmarketing data on Risperdol® as provided in the sponsor's N000 submission.

In accordance with the Clinical Review MAPP Section 4 summarizes the study design and overall numbers of subjects for each trial outlined above, and Seciton 7.2 enumerates subjects by treatment and by treatment duration (also provides some information on disposition and number of completers). To avoid redundancy, this information is not repeated in this section.

VII. Subjects Included for Safety Analyses for each Safety Dataset.

It is important to note that safety data analyzed for a given safety dataset were from subjects that were in the ITT safety population (defined as subjects receiving at least one dose of study medication using an LOCF approach for a given clinical parameter when examining group mean change or treatment endpoint values for given parameter and using a 5/31/05 cut-off date).

VIII. Coding Systems for AEs.

MEDRA System: Results on SAEs, ADOs, deaths and AEs described in the SCS are using the MEDRA system and events are reported using the Dictionary Term, unless otherwise specified.

WHO System : This system was used in the CSRs of at least the pivotal Phase III trials that were reviewed.

Reviewer Comment on AE Categorization Systems. *It appears that the SCS adopted the MedRA system which was more recently deemed by the Agency as the more acceptable method AE categorization, to the knowledge of the undersigned.*

IX. Schedule of Safety Assessments.

This topic will be discussed in relevant subsections below. Also refer to the Study Schedules provided in the Table Series 10.1 in the appendix of this review. Subsections below described time-points for specific clinical parameters.

X. Time-Windows of Safety Assessments for Each Study Visit

Visit/assessment time-windows were provided in the 2.7.4 SCS module of the original submission starting on page 265 of the Statistical Analyses Plan section of the SCS. Since these time-windows are important for interpreting safety data, a copy of the sponsor's tables showing the time intervals for each visit for each study is provided in the Table Series 10.5 in the appendix of this review.

Reviewer Comment and Caveat. *It is not clear if the above time-window tables reflect true time-windows or were provided in the case that assessments varied to the extent shown in the tables.*

Actual assessment time-points were likely to vary widely and vary widely relative to dosing across subjects at least for time-points when patients were outpatients. Subjects in the short-term Phase III and OL Phase III trials were outpatients, except for at least the first two weeks of

DB treatment in the short-term Phase III trials. Subjects were required to be inpatients during the first 2 weeks of DB treatment in the short-term trials and were outpatients thereafter, unless it was clinically indicated to prolong hospitalization or readmit a given subject. However, on PK assessment days subjects were generally inpatients (e.g. when PK sampling was conducted over multiple time-points on a given treatment day).

XI. Miscellaneous Topics

Exposure. This topic no longer appears before the safety results but instead, appears in Section 7.2.1 which follows the safety results and is entitled "Description of Primary Clinical Data Sources (Populations Exposed and Extend of Exposure) Used to Evaluate Safety." This major change in organization is in accordance to the MAPP for this review.

Demographic Features. According the MAPP, this topic is no longer covered here, but instead is provided after the safety results subsections in Section 7.2.1.2, entitled "Demographics."

XII. An Important Note to the Reader on Subsections 7.1.2-7.1.9

The Summary of Clinical Safety section (SCS) of the NDA generally did not describe individual subjects with SAEs or who had AEs leading to cessation of treatment in the in-text sections on the serious adverse events and adverse dropouts and in sections on the incidence of potentially clinically significant outliers. However, descriptions of individual subjects were found in some of the safety sections of CSRs of each short-term Phase III trial or were found upon review by the undersigned review of selected narratives. Also refer to Section 7.2.8 of this review regarding potential concerns with capturing clinically remarkable subjects or events.

Subsections on SAEs, ADOs and AEs (sections 7.1.2-3 and 7.1.5) of this review focus on the the incidence of SAEs, ADOs and AEs, respectively. Section 7.1.3.3. focuses on potentially clinically remarkable subjects covering specific organ system topics (and includes some ADOs and SAEs). The sponsor conducted special search strategies for potentially remarkable events which is provided under Section 7.1.4 of this review. These subsections on potential clinically remarkable events is not considered a comprehensive overview of such events and of all subjects with these type of event for reasons described in Section 7.2.8 of this review. Subsections on clinical parameters focus on results on the incidence of outliers and descriptive statistical results (sections 7.1.7-9).

7.1.1 Deaths

The following deaths include newly reported deaths in the 120-day SUR submission. Section 7.2.9 of this review describes safety results provided in the SUR in accordance with the Clinical

- 2 completed suicides (1 of these deaths occurred between [redacted] after the 5/31/05 cut-off date, such that the CIOMS report was provided instead of the CRF in the N000 submission)
  - Subject 200416 in Study -703 died after an overdose of venlafaxine and lorazepam on Day 238 of treatment (Day 1 corresponds to Day 1 of the 6-week DB lead-in Study -303).
  - Subject 20156 in Study -703 completed suicide described in the SUR as a 41 year old female who completed suicide by falling from the 3rd floor.
- Subject 200214: Bronchopneumonia in a 70 year old male subject. This OL Pal treated subject is discussed in more detail below.

Reviewer Comment and Conclusions on Reported Deaths. *No deaths occurred in the 4 completed Phase III trials, a few deaths occurred in the "prevention relapse" Phase III trial (Study -3010 which is ongoing and in the OL extension trials. No deaths occurred in the Phase I/II trials. The deaths in Pal treated subjects were primarily related to suicidality (except 1 death was reported as bronchopneumonia). Completed suicide was reported in one placebo subject, noting that the sample size of Pal exposure far exceeds the total number of subjects exposed to placebo in these trials.*

Suicidality, including successful suicide or lethal attempts is not uncommon in this patient population. The completed suicides reported in trials, as above, could have been associated with in part, due to lack-of-efficacy of the blinded study drug (placebo or paliperidone) and/or to the underlying pre-existing condition. Suicidality is also believed by psychiatric professionals to be associated with improvement of symptoms in some patients, such as in a subject who develops more insight that they have schizophrenia which can occur in patients who improve with treatment and as they realize the serious, debilitating and chronic nature of their illness. Off-label treatment with antidepressant medications, as well as the addition of other therapeutic modalities are generally provided to the treatment regimen in such patients to target suicidality and related symptomatology, as well as addressing social factors. It is well known that patients with schizophrenia are at risk of suicidality which may increase as symptoms improve. It is also part of good clinical practices to monitor patients for suicidality and to treat patients accordingly. The sponsor also provides a special safety section on this topic that will be summarized under subsection 2.6.1.

Suicides were only reported in subjects in the longer-term, 6-12 month OL trials, including Study -301 which involved several months of treatment, but were not reported in any of the short-term trials that included placebo, Pal and other active treatment groups. Not only were subjects of the longer term trials (OL trials and study -301) followed over months of treatment in which more events are likely to occur, but also the sample size of subjects in these studies was large in which all of these subjects received OL Pal (except for a short DB phase in Study -301). In contrast to these longer term trials of OL Pal subjects, the sample size of placebo controlled subjects in the shorter-term trials Phase III studies (combined) is much smaller. Consequently it is not surprising that no suicides occurred in the small number of placebo subjects that were included in the short term trials. Both the sample size and the duration of the shorter-term DB

studies were probably insufficient to generate a baseline suicide signal that is known to exist in this patient population.

Finally, the only DB treated subject in DB placebo controlled trials that completed suicide was a placebo treated subject, as reported in a subsequent 120-day SUR submission (subject 100846 in the longer term, Study -301 which was a "prevention of recurrence" study that included a short phase of DB placebo controlled treatment).

One death of "gun shot wound" was also reported in a subject on blinded study drug (the "completed suicide" or other terms related to suicidality were not used as the reported term for this subject). If the gun shot wound were not related to suicidality but rather indirectly due to homicidality or agitation, then this event alone does not provide adequate evidence for a drug-related safety signal for homicidality and is the type of event that is not unexpected for the patient population (homicidality and agitation can commonly occur in patients with schizophrenia and can lead to violent behaviors in some patients). Also refer to Section 9 for additional comments and recommendations regarding suicidality. The sponsor also provides a special safety section on this topic (of agitation and of suicidality) that will be summarized under subsection 7.1.4 of this review. Additionally suicidality is discussed in other sections of this review (e.g. see Section 7.1.3.3 focusing on subjects with specific types of clinically significant adverse events which includes a topic on suicidality).

Death due to bronchopneumonia (as above) occurred in one subject. Since this is an isolated case among a large number of exposed subjects, this finding alone does not provide adequate basis for suspecting a drug-related signal. Furthermore, the clinical scenario was very complicated by this patient's extensive past medical history and concomitant medications suggesting that his death was due to pre-existing multiple conditions. Yet, a role of Pal is serious considered in this case because of Pal's cardiovascular effects including QT prolongation to which this patient was likely at greater risk in experiencing from both a PK perspective (may have had higher Cmax, AUC exposure secondary to other factors that may have altered PK), as well as from a PD perspective (likely to have greater vulnerability to adverse effects given his baseline condition). The narrative does not describe vital sign results on this subject but his risk for myocardial ischemia and reduced cardiac output may have been increased (the first reported AE during treatment was myocardial ischemia on Day 8) secondary to Pal effects on the cardiovascular system (e.g. tachycardia, blood pressure changes that are more likely to occur early in treatment). Although QT prolongation was not reported until Day 111 the timing of assessments relative to dosing and the frequency of assessments can impact on capturing potentially maximal QT prolongation effects. Therefore, it is difficult to determine if QT prolongation was drug-related or related to his underlying history of QT prolongation. This single complicated subject is not alone sufficient evidence that Pal is not adequately safe. However, this review does raise the issue of a potential role of Pal in subjects at risk for cardiovascular and cardiac-related events that is discussed further in other relevant sections.

Refer to Section 9 for further reviewer comment and recommendations.

Narrative description of Subject 200214 copied from the 210-Day SUR submission (with selected words bolded by the undersigned reviewer).

Subject 200214 (Study R076477-SCH-702) was a **70-year-old man** who completed **double-blind treatment with placebo** before entering **the open-label extension, where he received ER OROS paliperidone 6 mg/day for the first week and 9 mg/day for another 15 weeks.** This subject had a history of prolonged QTc, and **pretreatment QTcLD values up to 464 ms** upon entering the double-blind study. Other **relevant medical history** included **chronic bronchitis, hypertension, ischemic disease in leg, cholelithiasis, and paresis nerve peroneus.** The subject was a **current smoker with a 40-year history** of smoking.

At **open-label baseline prior to receiving ER OROS paliperidone, the ECG was suggestive of myocardial ischemia.** During the open-label extension, the subject had adverse events of **myocardial ischemia on Day 8 of the open-label study**, a fungal infection of the foot on Day 19 of open-label treatment, and osteoarthritis on Day 20 of open-label treatment; all of these events were persisting when study drug was discontinued. **Concomitant medications** included acetylsalicylic acid for ischemic heart disease, potassium carbonate and mycoseptin (itraconazole) for foot mycosis, piracetam for prevention of vascular dementia, pentoxifylline for vasodilation of peripheral blood vessels, allopurinol to prevent **hyperuricemia, felodipine for hypertension**, and nimesulide for hip arthiritis.

Two ECGs were performed on **Day 111** of open-label treatment (the last day of study drug intake), and both revealed prolonged QTcLD intervals (503 and 513 ms) (Appendix 7.2.10). **Study medication was discontinued because of this adverse event,** which the investigator considered of doubtful relationship to study drug. **The following day, the subject's QTcLD value was 478 ms.** A laboratory evaluation performed on Day 112 of open-label treatment showed normal values for relevant laboratory parameters, including potassium (4.8 mmol/L; normal range, 3.40 to 5.40 mmol/L).

The subject died of bronchopneumonia on [redacted] **4 days after receiving the last dose of study medication** (see Section 2.1.2).

The QTcLD prolongation in this subject with a history of cardiovascular disorder and QTc prolongation was observed after 111 days of treatment with ER OROS paliperidone. The QTcLD values decreased within 24 hours despite the fact that t_{max} would have been reached 1 day after the last drug intake, it is therefore unlikely that this event is causally related to paliperidone.

7.1.2 Other Serious Adverse Events

This section describes serious adverse events (SAEs) as of the August 31, 2005 cut-off date, as reported in the N000 submission.

SAEs and ADOs provided in the 120-Day SUR was the primary source of review for the long term safety data which comes from ongoing OL trials. However, other sections on clinical safety parameters provide results as provided in the original NDA with updated results from the 120-

Day SUR that were provided in Section 7.2.9 of this review (in accordance with the Clinical Reviewer MAPP). Note that ICH guidelines for 6 month exposure were met in the OL dataset provided in the original NDA while ICH guidelines for 12 month exposure was met in the updated OL dataset in the 120-day SUR reported. Study -301 was completed in time for inclusion of safety data from this SUR, as well. Therefore, refer to section 7.2.9 of this review for a complete and updated information on SAEs and ADOs for Study -301 (and the OL extension study -701), as well as for the longer term safety dataset from OL extension trials. Only summary tables of SAEs and ADOs of ongoing Phase III trials are provided in subsections 7.1.2 and 7.1.3, respectively.

Descriptions of selected subjects (based on narratives) is not described in this section of the review since more complete and updated information was provided in the SUR submission. Also selected subjects are described in section 7.1.3.3 in order to provide a more comprehensive presentation of clinically remarkable subjects.

Some Potential Caveats Specific to the Phase III DB Dataset
Note that the most studies were conducted in a confined study unit (e.g. in most Phase I studies) or patients were hospitalized for at least 14 days during the DB phase of the Phase III trials. Thus, SAEs reported during these periods of hospitalization may reflect an under-representation of SAEs in an outpatient population (SAEs that would otherwise result in hospitalization in an outpatient setting that may not be considered as SAEs in an inpatient setting). However, subjects were not required to be hospitalized after the initial 14-day period of the 8-week DB treatment phase of Phase III trials, unless it was clinically indicated. Furthermore, OL extension studies generally did not require hospitalization or confinement to a study unit. Finally, the overall number of paliperidone subjects was large in Phase III trials including trials involving 6-12 months duration (with 506 subject who had 6 months exposure as of the 5/31/05 cut-off date).

Also note that the 15 mg treatment group (employed in only 1 Phase III study) started subjects on 12 mg daily for one week before they received their assigned 15 mg daily dose-level for the remainder of the 6-week DB phase.

A Summary of Results on the Incidence of SAEs in Clinical Trials and Reviewer Comments and Conclusions
The following summarizes the sponsor's results (from the undersigned reviewer's perspective) based on the results found in the SCS sections on SAEs which focused on the incidence of events and as shown later in the subsection.

The incidence of SAEs for any given type of event (by Preferred Term category) ranged from 0% to 1% in treatment groups in each of the safety datasets of completed Phase I-III trials with few exceptions as follows:

- *Psychotic disorder (3 to 5%) and schizophrenia (3%) in paliperidone subjects of ongoing OL paliperidone non-placebo controlled extension trials. These SAEs occurred among 391 subjects who received 3 months or less of treatment and among*

776 subjects who received 3-12 months of treatment. The majority of these subjects received at least 6 months of treatment.

The incidence in placebo treated subjects on a given type of event (by Preferred Term category) in safety datasets of placebo controlled, parallel group, trials was similar to that of the paliperidone subjects. The SAEs that had an incidence that was numerically less that that of of the placebo subjects only showed a between-group differences of only 1or 2% (when comparing each Pal group to and placebo subjects).

The majority of SAEs (by Preferred Terms) in all Phase I-III trial safety datasets (includes ongoing trials) were either expected events given the study population or were expected given the known safety profile of Ris® (refer to approved labeling) and for the drug class (e.g. tachycardia associated with orthostatic hypotension, extrapyramidal system related AEs).

Psychotic-related SAEs are expected for the patient population. The incidence between placebo and pal groups and across dose-levels in the Phase III trials for these type of SAEs were similar (as shown in a summary table provided later in this section). It is also notable that psychotic related SAEs did not appear to be greater in the 3 mg Pal group (the lowest dose-level) than in the other Pal groups (at 6, 9, 12 and 15 mg) or compared to the placebo group. Refer to Section 6 for results and comments related to subject disposition and for the incidence of subjects who dropped out early due to lack of efficacy.

Several SAEs were isolated events (by Preferred Term). Generally, such isolated SAEs are not considered as adequate evidence for suspecting an new, unexpected, clinically remarkable drug effect on the basis of the given isolated case, alone (e.g. this applies to an isolated SAE which occurred in only 1 subject in a paliperidone group in a given safety dataset that was not observed in other paliperidone groups, or was also observed in placebo or olanzapine subjects, or occurred in a low dose paliperidone group and not at higher dose-levels in the fixed dose trials, combined).

There can be exceptions in which an isolated SAE may be highly suspicious of a drug effect on the basis of a given event that cannot be accounted for by other non-drug-related factors or on the basis of supporting evidence obtained elsewhere (e.g. based on other safety data described in this review, the potential for a similar safety signal suggested by similar events reported for related drugs, among other considerations). An effort was made by the undersigned reviewer to find such cases. Refer to section 7.1.3.3 of this review for a discussion of individual subjects that may fall under this category.

Refer to the final section of this review for further comments and recommendations.

The remainder of this subsection is to provide results of the incidence of SAEs in clinical safety datasets, as presented in the SCS which are the basis of conclusions and comments above.

Completed Phase III Trials -302, -303, -304 and -305.

The table below summarizes SAEs (dictionary term) in the 3 pivotal Phase III 6-week trials, as provided by the sponsor.

Table 31: Serious Adverse Events
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
Body System or Organ Class	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)	15 mg (N=113)	Total (N=963)	10 mg (N=364)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. subjects with serious AE	23 (6)	7 (6)	15 (6)	13 (5)	14 (6)	6 (5)	55 (6)	22 (6)
Psychiatric disorders	18 (5)	6 (5)	9 (4)	10 (4)	7 (3)	5 (4)	37 (4)	18 (5)
Psychotic disorder	7 (2)	3 (2)	3 (1)	4 (2)	2 (1)	2 (2)	14 (1)	6 (2)
Schizophrenia	8 (2)	2 (2)	3 (1)	2 (1)	5 (2)	1 (1)	13 (1)	6 (2)
Agitation	0	0	4 (2)	2 (1)	1 (<1)	0	7 (1)	2 (1)
Suicidal ideation	1 (<1)	1 (1)	2 (1)	1 (<1)	1 (<1)	1 (1)	6 (1)	2 (1)
Aggression	1 (<1)	0	1 (<1)	0	2 (1)	0	3 (<1)	2 (1)
Acute psychosis	0	0	0	1 (<1)	0	0	1 (<1)	0
Anxiety	1 (<1)	0	0	0	0	1 (1)	1 (<1)	0
Depression	0	0	0	1 (<1)	0	0	1 (<1)	0
Hallucination, auditory	0	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Schizophrenia, paranoid type	0	0	1 (<1)	0	0	0	1 (<1)	0
Suicide attempt	1 (<1)	0	0	1 (<1)	0	0	1 (<1)	2 (1)
Hallucination	1 (<1)	0	0	0	0	0	0	0
Impaired self-care	0	0	0	0	0	0	0	1 (<1)
Sleep disorder	0	0	0	0	0	0	0	1 (<1)
Cardiac disorders	0	0	2 (1)	1 (<1)	3 (1)	0	6 (1)	2 (1)
Tachycardia	0	0	1 (<1)	1 (<1)	2 (1)	0	4 (<1)	1 (<1)
Bradycardia	0	0	0	0	1 (<1)	0	1 (<1)	0
Sinus tachycardia	0	0	1 (<1)	0	0	0	1 (<1)	0
Cardio-respiratory arrest	0	0	0	0	0	0	0	1 (<1)
Investigations	2 (1)	0	1 (<1)	0	2 (1)	2 (2)	5 (1)	1 (<1)
Blood creatine phosphokinase increased	0	0	1 (<1)	0	0	0	1 (<1)	0
Blood glucose increased	0	0	0	0	0	1 (1)	1 (<1)	0
Blood lactate dehydrogenase increased	0	0	1 (<1)	0	0	0	1 (<1)	0
Blood pressure increased	0	0	0	0	1 (<1)	0	1 (<1)	0
Electrocardiogram QT corrected interval prolonged	0	0	0	0	1 (<1)	0	1 (<1)	0

Table 31: Serious Adverse Events (continued)
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
Body System or Organ Class	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)	15 mg (N=113)	Total (N=963)	10 mg (N=364)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Investigations (continued)								
Heart rate irregular	0	0	0	0	1 (<1)	0	1 (<1)	0
Weight increased	0	0	0	0	0	1 (1)	1 (<1)	0
Electrocardiogram QT prolonged	0	0	0	0	0	0	0	1 (<1)
Electrocardiogram T wave abnormal	1 (<1)	0	0	0	0	0	0	0
Liver function test abnormal	1 (<1)	0	0	0	0	0	0	0
Nervous system disorders	0	0	1 (<1)	0	3 (1)	1 (1)	5 (1)	0
Akathisia	0	0	0	0	0	1 (1)	1 (<1)	0
Convulsion	0	0	0	0	1 (<1)	0	1 (<1)	0
Dizziness	0	0	0	0	1 (<1)	0	1 (<1)	0
Dystonia	0	0	0	0	1 (<1)	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Gastrointestinal disorders	0	0	1 (<1)	1 (<1)	0	0	2 (<1)	0
Duodenal perforation	0	0	1 (<1)	0	0	0	1 (<1)	0
Gastrointestinal haemorrhage	0	0	0	1 (<1)	0	0	1 (<1)	0
Metabolism and nutrition disorders	1 (<1)	0	0	2 (1)	0	0	2 (<1)	1 (<1)
Diabetes mellitus	0	0	0	1 (<1)	0	0	1 (<1)	0
Hypoglycaemia	0	0	0	1 (<1)	0	0	1 (<1)	0
Water intoxication	0	0	0	1 (<1)	0	0	1 (<1)	0
Electrolyte imbalance	0	0	0	0	0	0	0	1 (<1)
Polydipsia	1 (<1)	0	0	0	0	0	0	0
Vascular disorders	0	0	0	1 (<1)	1 (<1)	0	2 (<1)	0
Hypotension	0	0	0	1 (<1)	1 (<1)	0	2 (<1)	0
General disorders and administration site conditions	0	1 (1)	0	0	0	0	1 (<1)	0
Drug ineffective	0	1 (1)	0	0	0	0	1 (<1)	0
Immune system disorders	0	0	1 (<1)	0	0	0	1 (<1)	0
Anaphylactic reaction	0	0	1 (<1)	0	0	0	1 (<1)	0
Infections and infestations	0	0	0	0	1 (<1)	0	1 (<1)	0
Cellulitis	0	0	0	0	1 (<1)	0	1 (<1)	0

Renal and urinary disorders	0	0	0	1 (<1)	0	0	1 (<1)	0
Renal failure acute	0	0	0	1 (<1)	0	0	1 (<1)	0
Renal impairment	0	0	0	1 (<1)	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	1 (<1)	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Chronic obstructive airways disease exacerbated	0	0	0	0	1 (<1)	0	1 (<1)	0
Aspiration	0	0	0	0	0	0	0	1 (<1)
Chronic obstructive pulmonary disease	1 (<1)	0	0	0	0	0	0	0
Social circumstances	0	0	1 (<1)	0	0	0	1 (<1)	0
Drug abuser	0	0	1 (<1)	0	0	0	1 (<1)	0
Injury, poisoning and procedural complications	1 (<1)	0	0	0	0	0	0	3 (1)
Drug toxicity	0	0	0	0	0	0	0	1 (<1)
Overdose	0	0	0	0	0	0	0	1 (<1)
Thermal burn	1 (<1)	0	0	0	0	0	0	0
Treatment noncompliance	0	0	0	0	0	0	0	1 (<1)

Cross-reference: Appendix 2.7.4.3.8.1.1.

Detailed Description of Selected SAEs

The following are descriptions of SAEs (some also were ADOs) that are not described elsewhere in this review but are of SAEs previously discussed as occurring in the Phase III trials. These descriptions are based on in-text information found in the CSRs of each of the 3 short-term Phase III trials. These SAEs are described under subheadings that correspond with those previously discussed.

Suicidality.

In study -304 Pal subjects 300306 and 300376 are described who abused cocaine with another substance (marijuana in one subject and alcohol in the other subject). One subject had a history of substance abuse. It is not clear from the description if the other subject had a history of substance abuse. These drugs are known to be associated with increased risk for suicidality and depressive symptoms. It is important to note that subjects were reported to have no history of suicidality. One of these 2 subjects (300306) also had a recent and significant stressor (death of a cousin) that occurred prior to his reported suicidal ideations. Suicidality resolved with "treatment." Both subjects had suicidal ideations but actual suicidal attempts are not described. It is likely that the suicidality in these subjects was related to the abuse or use of substances combined with other non-drug-related factors (stressors, underlying risk factors known to exist for this patient population).

Another subject (S300011) had suicidal ideation (suicidal attempt is not described), along with increased psychosis. Pal treatment was discontinued due to lack of efficacy. The subject's events resolved with "treatment." This subject, as well as the above subjects did not have a history of suicidality. The suicidality in S300011 is likely to be related to exacerbation of psychosis (due to lack of efficacy) and given that suicidality is common in this population.

See section 7.1.4.6 for a special search for suicidality related AEs conducted by the sponsor.

Elderly Phase III Study -302. Only 2 out of 76 Paliperidone subjects had SAEs in the elderly Phase III trial, Study -302 (3%; dictionary term of acute coronary syndrome in 1 subject and mania in another subject) in contrast to 8/38 placebo subjects (8%) in this trial (1 of these subjects had cardiac arrest reported

Ongoing Phase III Trial -301.
Study drug is still blinded in the ongoing placebo controlled Phase III "prevention of recurrence" Study -301 involving an 8-weeks OL-run-in phase, then a 6-week OL stabilization phase, followed by a DB treatment phase of variable duration in patients with schizophrenia.

This study was ultimately completed prior to the 120-Day SUR submission and unblinded safety results from this study were provided in the SUR. See section 7.2.9 for the incidence of SAEs and ADOs in treatment groups in this study.

Reviewer comment. *Study drug remains blinded such that the interpretation of results are difficult.*

The 2 most prominent signals are suicidality (including attempts and one completed suicide) and psychotic-related events. These events are not unexpected for the study population and were also observed in clinical trials of Risperidone (refer to approved labeling). However, the study drug assignment remains blinded so that actual incidence in actively treated subjects and a comparison to placebo treatment cannot be determined.

The subject with thrombocytopenia is described in Section 7.1.3.3. of this review.

The following summarizes reported SAEs as of the May 31, 2005 cut-off date among a total of 41 subjects with SAEs (see Section 7.2.9 for unblinded and updated information:

- 31 with psychotic related AEs (e.g. pscychotic disorder, worsening of schizophrenia, among others
- 4 suicide-related SAEs (one is a previously listed completed suicide under section 7.1.2, a suicide attempt, and suicidal ideation and an ADO reported as an SAE of a suicide attempt that was an overdose).
- 1 neuroleptic malignant syndrome SAE associated with increased creatine phosphokinase (CPK) of which "no additional information is available at this time."

- SAEs that resulted in ADOs (occurring in 1 subject each): overdose suicide attempt, as mentioned above, cholelithiasis, phlebothrombosis, thrombocytopenia and 1 subject that had SAEs of hypertensive crisis, non-cardiac chest pain and tachycardia.

The following summarizes reported SAEs between June 1, 2005 and August 31, 2005(only COMIS forms are provided for these subjects):

9 subjects with SAEs: 1 of whom died of completed suicide (see subsection on deaths) and the remaining 8 subjects had psychotic-related symptoms or conditions, that the sponsor indicated as being the result of an exacerbation of their underlying condition.

Ongoing Phase III Open Label Trials -701, -702, -703, -704, and -705.

Note the following: *Safety results from the OL extension trial dataset were provided for treatment subgroups by duration of exposure as follows:*

- *Treatment groups were subdivided on the basis of DB treatment assignment in the lead-in studies as follows: DB Placebo/OL Pal, DB Pal/OL Pal, DB olanzapine/OL Pal and total OL Pal subjects (which consists of all subjects independent of DB treatment assignment).*
- *Each of the above treatment groups were subdivided on the basis of duration of exposure as follows: into ≤ 3 month and > 3 month exposure subgroups in the N000 submission (and into ≤ 6 month and > 6 month subgroups in the 120-Day SUR as shown in Section 7.2.9 of this review).*

The following table summarizes results on SAEs in ongoing OL extension trials -702, -703, -704, and -705, as of the 5/31/05 cut-off date (while results of OL extension trial -701 are provided thereafter in this subsection). See section 7.2.9 for an updated incidence of SAEs and ADOs in treatment groups in these trials, combined.

Table 33: Serious Adverse Events Through 31 May 2005
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)

Total no. subjects with serious adverse events	15 (14)	8 (6)	19 (11)	48 (10)	20 (19)	22 (15)	54 (14)	78 (10)
Psychiatric disorders	11 (10)	6 (5)	14 (8)	41 (8)	18 (17)	18 (13)	43 (11)	65 (8)
Psychotic disorder	6 (6)	2 (2)	7 (4)	15 (3)	6 (6)	10 (7)	19 (5)	27 (3)
Schizophrenia	2 (2)	1 (1)	3 (2)	19 (4)	8 (8)	6 (4)	13 (3)	26 (3)
Depression	0	2 (2)	1 (1)	3 (1)	0	2 (1)	1 (<1)	7 (1)
Suicidal ideation	2 (2)	1 (1)	1 (1)	5 (1)	0	0	3 (1)	6 (1)
Agitation	2 (2)	0	1 (1)	4 (1)	7 (7)	0	10 (3)	4 (1)
Suicide attempt	1 (1)	1 (1)	0	2 (<1)	0	1 (1)	1 (<1)	4 (1)
Hallucination, auditory	0	0	0	2 (<1)	0	0	0	2 (<1)
Acute psychosis	0	0	0	1 (<1)	0	0	0	1 (<1)
Completed suicide	0	0	0	0	0	1 (1)	0	1 (<1)
Delusion	0	0	1 (1)	1 (<1)	0	0	1 (<1)	1 (<1)
Depressed mood	0	0	0	1 (<1)	0	0	0	1 (<1)
Insomnia	0	0	0	1 (<1)	2 (2)	0	2 (1)	1 (<1)
Paranoia	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Aggression	2 (2)	0	0	0	3 (3)	0	5 (1)	0
Confusional state	0	0	0	0	1 (1)	0	1 (<1)	0
Delusional disorder, persecutory type	0	0	1 (1)	0	0	0	1 (<1)	0
Disorientation	0	0	1 (1)	0	0	0	1 (<1)	0
Self-injurious ideation	0	0	0	0	1 (1)	0	1 (<1)	0
Infections and infestations	0	0	1 (1)	4 (1)	0	2 (1)	1 (<1)	6 (1)
Nasopharyngitis	0	0	0	2 (<1)	0	0	0	2 (<1)
Bronchitis acute	0	0	0	1 (<1)	0	0	0	1 (<1)
Pneumonia	0	0	0	0	0	1 (1)	0	1 (<1)
Pulmonary tuberculosis	0	0	0	0	0	1 (1)	0	1 (<1)
Urinary tract infection	0	0	0	1 (<1)	0	0	0	1 (<1)
Hepatitis A	0	0	1 (1)	0	0	0	1 (<1)	0
Nervous system disorders	1 (1)	2 (2)	3 (2)	3 (1)	1 (1)	0	5 (1)	5 (1)
Dizziness	0	0	0	3 (1)	0	0	0	3 (<1)
Dystonia	0	1 (1)	0	0	0	0	0	1 (<1)
Ischaemic stroke	0	1 (1)	0	0	0	0	0	1 (<1)
Akathisia	0	0	0	0	1 (1)	0	1 (<1)	0
Coordination abnormal	0	0	1 (1)	0	0	0	1 (<1)	0
Dysarthria	0	0	1 (1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (1)	0	0	0	1 (<1)	0
Transient ischaemic attack	1 (1)	0	0	0	0	0	1 (<1)	0

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Appendix 2.7.4.3.8.1.3.

Table 33: Serious Adverse Events Through 31 May 2005 (continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

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Injury, poisoning and procedural complications	1 (1)	1 (1)	1 (1)	2 (<1)	0	1 (1)	2 (1)	4 (1)
Fall	0	0	0	1 (<1)	0	0	0	1 (<1)
Intentional misuse	0	0	0	1 (<1)	0	0	0	1 (<1)
Overdose	0	0	0	0	0	1 (1)	0	1 (<1)
Road traffic accident	0	1 (1)	0	0	0	0	0	1 (<1)
Accidental overdose	0	0	1 (1)	0	0	0	1 (<1)	0
Alcohol poisoning	1 (1)	0	0	0	0	0	1 (<1)	0
General disorders and administration site conditions	0	0	0	3 (1)	1 (1)	0	1 (<1)	3 (<1)
Chills	0	0	0	1 (<1)	0	0	0	1 (<1)
Cyst	0	0	0	1 (<1)	0	0	0	1 (<1)
Pyrexia	0	0	0	1 (<1)	0	0	0	1 (<1)
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0
Investigations	0	0	0	2 (<1)	0	0	0	2 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood and lymphatic system disorders	0	0	0	1 (<1)	0	0	0	1 (<1)
Anaemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Metabolism and nutrition disorders	0	0	1 (1)	1 (<1)	0	0	1 (<1)	1 (<1)
Diabetes mellitus	0	0	0	1 (<1)	0	0	0	1 (<1)
Hypokalaemia	0	0	1 (1)	0	0	0	1 (<1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	1 (1)	0	1 (<1)
Benign neoplasm of skin	0	0	0	0	0	1 (1)	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	0	0	1 (1)	0	0	1 (1)	1 (<1)	1 (<1)
Asthma	0	0	0	0	0	1 (1)	0	1 (<1)
Dyspnoea	0	0	1 (1)	0	0	1 (1)	1 (<1)	1 (<1)
Cardiac disorders	1 (1)	0	2 (1)	0	2 (2)	0	5 (1)	0
Bundle branch block	1 (1)	0	0	0	0	0	1 (<1)	0
Myocardial infarction	0	0	1 (1)	0	0	0	1 (<1)	0
Sinus tachycardia	0	0	0	0	1 (1)	0	1 (<1)	0
Tachycardia	0	0	1 (1)	0	1 (1)	0	2 (1)	0
Gastrointestinal disorders	1 (1)	0	0	0	0	0	1 (<1)	0
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Social circumstances	0	0	0	0	1 (1)	0	1 (<1)	0
Drug abuser	0	0	0	0	1 (1)	0	1 (<1)	0

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Appendix 2.7.4.3.8.1.3.

SAEs in the Ongoing OL Extension study -701 (as of 5/31/2005):
2 subjects receiving OL Paliperidone had psychotic related SAEs ("recurrence of schizophrenia" and "exacerbation of paranoid schizophrenia").

The following are additional SAEs between cut-off dates of [redacted] for all of the above OL extension trials -701 through -705 (only the CIOMS forms are provided by the sponsor for these more recent SAEs):

- 1 subject died who committed suicide (see previous section on deaths).
- 1 subject died of bronchopneumia (see previous section on deaths).
- Most of the remaining SAEs (27 subjects) were hosptitalizations due to pshchotic-related symptoms/conditions. Other SAEs were "unrelated medical conditions," and "less frequently, SAEs of "drug-related" events such as extrapyramidal symptoms and syncope.

Section 7.2.9 of this review provides updated safety information on SAEs and ADOs from the -701 trial.

Phase I/IIa Studies.
Reviewer Comment. *Few SAEs were reported among all Phase I/IIa trials and did not reveal any new or unexpected findings from that previously described in this review. 1 subject had myocardial infarction. Respiratory distress associated with extrapyramidal symptoms is not unexpected and is described in labeling.*

17 Healthy Subject Phase I/IIa Studies. No SAEs were reported among the 17 healthy subject Phase I/IIa studies (275 paliperidone treated subjects and 222 subjects treated with other formulations or medications in the ITT population of these trials combined).

3 Schizophrenia Phase I/IIa Trials. Only 3 subjects had SAEs (psychotic-related events, of which 1 subject was receiving risperidone treatment) in the 3 schizophrenia Phase I/IIa studies (out of 111 Paliperidone subjects, 34 immediate-release (IR) paliperidone subjects, and 55 risperidone subjects in the ITT population).

7 Other Phase I/IIa Trials. Reported SAEs were as follows:

3 IR paliperidone subjects: dystonia in 1 subject, extrapyramidal disorder and respiratory distress in another subject, and myocardial infarction in the third subject (the former two subjects had treatment discontinued). Subject numbers could not be found for these subjects.

A search for "respiratory distress" and "myocardial infarction" among the Phase I/II narratives in the appendix to the SCS revealed the following 2 narratives (coped from the submission):

Subject 109047 (extrapyramidal disorder, respiratory distress), a 46-year-old man with schizoaffective disorder, enrolled in the study with a

history of asthma, hypertension, anxiety, insomnia, and suicide attempt by drug overdose. Prestudy, the subject received quetiapine for the treatment of psychosis which was discontinued on Day -13 of the screening period. During the screening period, the subject received lorazepam for anxiety, paracetamol for headache, and zolpidem tartrate for insomnia. The subject was randomly assigned to the IR paliperidone treatment group. No adverse events were reported after administration of placebo on Day 1 or after administration of 4 mg IR paliperidone on Day 2. After administration of 6 mg IR paliperidone on Day 3, the subject experienced severe respiratory distress and extrapyramidal disorder involving a swollen tongue and neck spasms, both considered by the investigator to be of very likely relationship to study drug. Diphenhydramine hydrochloride 50 mg and benztropine mesylate 2 mg were administered for the treatment of the extrapyramidal disorder that resolved in 3 hours; oxygen was administered for respiratory distress, which resolved 1 hour later. The subject was taken to the emergency room as a precaution, but was not admitted in the hospital. The subject was discontinued from the study due to respiratory distress and the extrapyramidal disorder. The subject remained at the study hospital 3 days after discontinuation from the study for stabilization. These events were reported as serious.

7.1.3 Dropouts and Other Significant Adverse Events

Reviewer summary and comment. *Results on the incidence of the incidence of ADOs were generally similar to results of SAEs (see reviewer summary and comments under 7.1.2) with 0-1% incidence observed in Paliperidone and placebo groups (by Peferred Term categories) with a few exceptions described in paragraphs that follow. The majority of events were not unexpected and/or showed a similar incidence between placebo and paliperidone groups and did not show a clear or consistent dose-dependent effect, similar to that observed with SAEs. As observed with SAEs, a few isolated ADOs occurred in paliperidone subjects that do not provide a basis for suspecting an unexpected or new drug-related event on the basis of these observations alone (e.g. the Preferred Term ADO occurred in only 1 subject who was in a paliperidone group but was not observed in other paliperidone groups, or was also observed in placebo or olanzapine subjects, or occurred in a low dose paliperidone group and not at higher dose-levels in the fixed dose trials, combined).*

The short term efficacy trial of elderly subjects (Study -302) was an exception regarding the above observations. 3% of Paliperidone subjects were ADOs due to QT prolongation and an additional Paliperidone subject was an ADO due to acute coronary syndrome while none of the placebo subjects had any cardiac-related events leading to ADOs. However, the sample size was small (only needed 2 subjects to have an incidence of 3%).

Adverse Dropouts.
This section describes adverse dropouts (ADOs), otherwise referred to premature withdrawal from the study due to an AE (the sponsor used August 31, 2005 as the reporting cut-off date).

Reviewer Comment and Conclusions on ADOSs in Clinical Trials.
Group differences on the incidence of ADOs are generally not apparent, as the incidence in any given group is small. Nervous system disorder ADOs showed a slightly greater incidence in Pal subjects than placebo subjects but the difference is only by 1 to 2%, which could be due to chance alone given the number of dependent variables. Refer to Section 7.1.3.3 describing potentially clinically remarkable subjects.

Completed Phase III Trials -303, -303 and -305.
The table below summarizes ADOSs in the 3 pivotal Phase III 6-week trials, as provided by the sponsor.

Table 34: Adverse Events Leading to Study Discontinuation
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
Body System or Organ Class	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)	15 mg (N=113)	Total (N=963)	10 mg (N=364)
Dictionary-derived Term	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. subjects who discontinued due to AE	18 (5)	3 (2)	15 (6)	10 (4)	13 (5)	4 (4)	45 (5)	20 (5)
Nervous system disorders	0	1 (1)	3 (1)	4 (2)	6 (2)	1 (1)	15 (2)	4 (1)
Dizziness	0	0	0	1 (<1)	1 (<1)	1 (1)	3 (<1)	0
Akathisia	0	0	0	2 (1)	0	0	2 (<1)	0
Headache	0	0	0	1 (<1)	1 (<1)	0	2 (<1)	0
Sedation	0	0	1 (<1)	0	1 (<1)	0	2 (<1)	1 (<1)
Tremor	0	0	1 (<1)	1 (<1)	0	0	2 (<1)	0
Convulsion	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Dystonia	0	0	0	0	1 (<1)	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Memory impairment	0	0	0	1 (<1)	0	0	1 (<1)	0
Parkinsonism	0	0	0	0	1 (<1)	0	1 (<1)	0
Somnolence	0	0	0	1 (<1)	0	0	1 (<1)	2 (1)
Syncope	0	1 (1)	0	0	0	0	1 (<1)	0
Psychiatric disorders	9 (3)	0	5 (2)	3 (1)	3 (1)	1 (1)	12 (1)	7 (2)
Psychotic disorder	1 (<1)	0	1 (<1)	2 (1)	2 (1)	1 (1)	6 (1)	2 (1)
Agitation	4 (1)	0	1 (<1)	1 (<1)	1 (<1)	0	3 (<1)	1 (<1)
Anorgasmia	0	0	0	1 (<1)	0	0	1 (<1)	0
Impulsive behaviour	0	0	1 (<1)	0	0	0	1 (<1)	0
Schizophrenia	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Suicidal ideation	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0
Aggression	0	0	0	0	0	0	0	1 (<1)
Hostility	0	0	0	0	0	0	0	1 (<1)
Insomnia	2 (1)	0	0	0	0	0	0	1 (<1)
Psychomotor agitation	1 (<1)	0	0	0	0	0	0	0
Suicide attempt	0	0	0	0	0	0	0	1 (<1)

Investigations	3 (1)	2 (2)	2 (1)	1 (<1)	3 (1)	1 (1)	9 (1)	6 (2)
Electrocardiogram QT corrected interval prolonged	1 (<1)	0	1 (<1)	0	1 (<1)	0	2 (<1)	0
Hepatic enzyme increased	0	1 (1)	1 (<1)	0	0	0	2 (<1)	0
Alanine aminotransferase increased	0	0	0	1 (<1)	0	0	1 (<1)	3 (1)
Blood glucose increased	0	0	0	0	0	1 (1)	1 (<1)	0
Blood pressure increased	0	0	0	0	1 (<1)	0	1 (<1)	0
Electrocardiogram ST-T change	0	1 (1)	0	0	0	0	1 (<1)	0

Cross-reference: Appendix 2.7.4.3.8.2.1.

(continued)

Table 34: Adverse Events Leading to Study Discontinuation (continued)
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg	Total	10 mg
Body System or Organ Class	(N=355)	(N=127)	(N=235)	(N=246)	(N=242)	(N=113)	(N=963)	(N=364)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Investigations (continued)								
Transaminases increased	0	0	0	0	1 (<1)	0	1 (<1)	0
Aspartate aminotransferase increased	0	0	0	0	0	0	0	3 (1)
Body temperature increased	1 (<1)	0	0	0	0	0	0	0
Electrocardiogram QT prolonged	0	0	0	0	0	0	0	2 (1)
Hepatic enzyme abnormal	1 (<1)	0	0	0	0	0	0	0
Liver function test abnormal	0	0	0	0	0	0	0	1 (<1)
Gastrointestinal disorders	0	0	4 (2)	2 (1)	1 (<1)	0	7 (1)	0
Nausea	0	0	1 (<1)	1 (<1)	1 (<1)	0	3 (<1)	0
Abdominal pain upper	0	0	0	1 (<1)	0	0	1 (<1)	0
Dry mouth	0	0	1 (<1)	0	0	0	1 (<1)	0
Duodenal perforation	0	0	1 (<1)	0	0	0	1 (<1)	0
Vomiting	0	0	1 (<1)	0	0	0	1 (<1)	0

Cardiac disorders	2 (1)	0	2 (1)	2 (1)	2 (1)	0	6 (1)	2 (1)
Tachycardia	1 (<1)	0	0	1 (<1)	2 (1)	0	3 (<1)	1 (<1)
Sinus tachycardia	0	0	1 (<1)	1 (<1)	0	0	2 (<1)	1 (<1)
Bundle branch block left	0	0	0	1 (<1)	0	0	1 (<1)	0
Palpitations	0	0	1 (<1)	0	0	0	1 (<1)	0
Bradycardia	1 (<1)	0	0	0	0	0	0	0
General disorders and administration site conditions	0	0	0	1 (<1)	0	1 (1)	2 (<1)	0
Asthenia	0	0	0	1 (<1)	0	0	1 (<1)	0
Feeling abnormal	0	0	0	0	0	1 (1)	1 (<1)	0
Vascular disorders	1 (<1)	1 (1)	0	1 (<1)	0	0	2 (<1)	0
Hypotension	0	1 (1)	0	0	0	0	1 (<1)	0
Ischaemia	0	0	0	1 (<1)	0	0	1 (<1)	0
Hypertension	1 (<1)	0	0	0	0	0	0	0
Eye disorders	0	0	0	0	1 (<1)	0	1 (<1)	0
Vision blurred	0	0	0	0	1 (<1)	0	1 (<1)	0
Immune system disorders	0	0	1 (<1)	0	0	0	1 (<1)	0
Anaphylactic reaction	0	0	1 (<1)	0	0	0	1 (<1)	0
Infections and infestations	0	0	1 (<1)	0	0	0	1 (<1)	0
Amoebic dysentery	0	0	1 (<1)	0	0	0	1 (<1)	0
Metabolism and nutrition disorders	1 (<1)	0	0	1 (<1)	0	0	1 (<1)	2 (1)
Water intoxication	0	0	0	1 (<1)	0	0	1 (<1)	0
Diabetes mellitus	0	0	0	0	0	0	0	1 (<1)
Electrolyte imbalance	0	0	0	0	0	0	0	1 (<1)
Hyponatraemia	1 (<1)	0	0	0	0	0	0	0
Polydipsia	1 (<1)	0	0	0	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	1 (1)	1 (<1)	0
Dysuria	0	0	0	0	0	1 (1)	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	1 (1)	1 (<1)	0
Dyspnoea	0	0	0	0	0	1 (1)	1 (<1)	0
Social circumstances	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0
Drug abuser	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0
Injury, poisoning and procedural complications	1 (<1)	0	0	0	0	0	0	1 (<1)
Overdose	0	0	0	0	0	0	0	1 (<1)
Thermal burn	1 (<1)	0	0	0	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	0	0	0	1 (<1)
Galactorrhoea	0	0	0	0	0	0	0	1 (<1)
Skin and subcutaneous tissue disorders	1 (<1)	0	0	0	0	0	0	0
Rash	1 (<1)	0	0	0	0	0	0	0

Cross-reference: Appendix 2.7.4.3.8.2.1.

A description of selected ADOs that were also SAEs in the short-term Phase III, completed trials (that were selected from in-text descriptions found in the CSRs) were covered in the previous section of this review on SAEs. The following are selected ADOs that were not SAEs that were revealed from a review of CSRs (in-text sections) in an effort to reveal potentially remarkable or new safety findings.

ADO associated with Elevated Liver Enzymes.

Elderly Phase III Study -302. The following table shows the incidence of ADOs in the elderly Study -302.

Table 35: Adverse Events Leading to Study Discontinuation (Study R076477-SCH-302)

Body System or Organ Class Dictionary-derived Term	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)
Total no. subjects who discontinued due to AE	3 (8)	5 (7)
Infections and infestations	1 (3)	2 (3)
Bronchopneumonia	0	1 (1)
Pneumonia	1 (3)	1 (1)
Investigations	0	2 (3)
Electrocardiogram QT corrected interval prolonged	0	2 (3)
Cardiac disorders	0	1 (1)
Acute coronary syndrome	0	1 (1)
Respiratory, thoracic and mediastinal disorders	0	1 (1)
Hydrothorax	0	1 (1)
Gastrointestinal disorders	1 (3)	0
Diarrhoea	1 (3)	0
Nervous system disorders	1 (3)	0
Status epilepticus	1 (3)	0

Cross-reference: Appendix 2.7.4.3.8.2.1.

Reviewer comment. *3% of Paliperidone subjects were ADOs due to QT prolongation and an additional Paliperidone subject was an ADO due to acute coronary syndrome while none of the placebo subjects had any cardiac-related events leading to ADOs. However, the study is small and only 2 subjects yields a 3% incidence in Paliperidone subjects.*

Ongoing Phase III Trial -301.
Study drug is still blinded in the ongoing placebo controlled Phase III "prevention of recurrence" Study -301 involving an 8-weeks OL-run-in phase, then a 6-week OL stabilization phase, followed by a DB treatment phase of variable duration in patients with schizophrenia (among

This study was ultimately completed prior to the 120-Day SUR submission and unblinded safety results from this study were provided in the SUR. See section 7.2.9 for the incidence of SAEs and ADOs in treatment groups in this study.

Ongoing Phase III Open Label Trials -702, -703, -704, and -705.
The following table summarizes results of Studies -702 through -705 (as provided by the sponsor, as of their cut-off date for the N000 submission). Refer to Section 7.2.9 for updated information from these ongoing trials.

Table 36: Adverse Events Leading to Study Discontinuation
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=166) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
Total no. subjects with adverse events	7 (7)	3 (2)	15 (8)	23 (5)	17 (10)	4 (3)	39 (10)	30 (4)
Psychiatric disorders	3 (3)	2 (2)	8 (4)	17 (3)	9 (8)	4 (3)	20 (5)	23 (3)
Depression	0	0	0	4 (1)	0	2 (1)	0	6 (1)
Insomnia	0	0	0	3 (1)	2 (2)	1 (1)	2 (1)	4 (1)
Schizophrenia	0	0	0	3 (1)	3 (3)	1 (1)	3 (1)	4 (1)
Suicidal ideation	1 (1)	0	1 (1)	3 (1)	2 (2)	0	4 (1)	3 (<1)
Anxiety	0	1 (1)	0	0	1 (1)	1 (1)	1 (<1)	2 (<1)
Hallucination, auditory	0	0	0	2 (<1)	0	0	0	2 (<1)
Psychotic disorder	2 (2)	0	3 (2)	1 (<1)	3 (3)	1 (1)	8 (2)	2 (<1)
Suicide attempt	0	0	0	2 (<1)	0	0	0	2 (<1)
Acute psychosis	0	0	0	1 (<1)	0	0	0	1 (<1)
Depressed mood	0	0	0	0	0	1 (1)	0	1 (<1)
Homicidal ideation	0	0	0	1 (<1)	0	0	0	1 (<1)
Hostility	0	0	0	1 (<1)	0	0	0	1 (<1)
Paranoia	0	1 (1)	1 (1)	0	0	0	1 (<1)	1 (<1)
Aggression	0	0	0	0	1 (1)	0	1 (<1)	0
Agitation	0	0	2 (1)	0	2 (2)	0	4 (1)	0
Confusional state	0	0	2 (1)	0	0	0	2 (1)	0
Delusion	0	0	1 (1)	0	1 (1)	0	2 (1)	0
Disorientation	0	0	1 (1)	0	0	0	1 (<1)	0
Nervous system disorders	1 (1)	1 (1)	4 (2)	2 (<1)	2 (2)	1 (1)	7 (2)	4 (1)
Akathisia	0	0	1 (1)	1 (<1)	0	1 (1)	1 (<1)	2 (<1)
Dyskinesia	0	1 (1)	0	0	0	0	0	1 (<1)
Dystonia	0	0	0	1 (<1)	0	0	0	1 (<1)
Extrapyramidal disorder	0	0	1 (1)	0	0	1 (1)	1 (<1)	1 (<1)
Mental impairment	0	0	0	0	0	1 (1)	0	1 (<1)
Coordination abnormal	0	0	1 (1)	0	0	0	1 (<1)	0
Dizziness	0	0	0	0	2 (2)	0	2 (1)	0
Dysarthria	0	0	1 (1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (1)	0	0	0	1 (<1)	0
Tremor	1 (1)	0	0	0	0	0	1 (<1)	0
Investigations	0	1 (1)	1 (1)	2 (<1)	2 (2)	0	3 (1)	3 (<1)
Alanine aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Aspartate aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-refereuce: Appendix 2.7.4.3.8.2.2.

(continued)

Table 36: Adverse Events Leading to Study Discontinuation (continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
Investigations (continued)								
Blood prolactin increased	0	1 (1)	0	0	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	0	0	0	1 (<1)	0	0	0	1 (<1)
Gamma-glutamyltransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Weight increased	0	1 (1)	0	0	0	0	0	1 (<1)
Electrocardiogram T wave abnormal	0	0	0	0	1 (1)	0	1 (<1)	0
Hepatic enzyme increased	0	0	0	0	1 (1)	0	1 (<1)	0
Weight decreased	0	0	1 (1)	0	0	0	1 (<1)	0
Reproductive system and breast disorders	0	0	0	2 (<1)	0	0	0	2 (<1)
Erectile dysfunction	0	0	0	2 (<1)	0	0	0	2 (<1)
Gastrointestinal disorders	1 (1)	0	0	1 (<1)	3 (3)	0	4 (1)	1 (<1)
Dysphagia	0	0	0	1 (<1)	0	0	0	1 (<1)
Constipation	0	0	0	0	1 (1)	0	1 (<1)	0
Nausea	0	0	0	0	1 (1)	0	1 (<1)	0
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Vomiting	0	0	0	0	2 (2)	0	2 (1)	0
Injury, poisoning and procedural complications	1 (1)	0	1 (1)	1 (<1)	0	0	2 (1)	1 (<1)
Intentional misuse	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (1)	0	0	0	1 (<1)	0
Self mutilation	1 (1)	0	0	0	0	0	1 (<1)	0
Musculoskeletal and connective tissue disorders	1 (1)	0	0	1 (<1)	2 (2)	0	3 (1)	1 (<1)
Muscle rigidity	0	0	0	1 (<1)	0	0	0	1 (<1)
Arthralgia	0	0	0	0	1 (1)	0	1 (<1)	0
Joint stiffness	1 (1)	0	0	0	0	0	1 (<1)	0
Muscle twitching	0	0	0	0	1 (1)	0	1 (<1)	0

Skin and subcutaneous tissue disorders	0	0	0	1 (<1)	0	0	0	1 (<1)
Acne	0	0	0	1 (<1)	0	0	0	1 (<1)
Cardiac disorders	1 (1)	0	3 (2)	0	2 (2)	0	6 (2)	0
Myocardial infarction	0	0	1 (1)	0	0	0	1 (<1)	0
Myocardial ischaemia	0	0	1 (1)	0	0	0	1 (<1)	0
Palpitations	0	0	0	0	1 (1)	0	1 (<1)	0
Sinus tachycardia	1 (1)	0	0	0	1 (1)	0	2 (1)	0
Tachycardia	0	0	1 (1)	0	0	0	1 (<1)	0
Eye disorders	0	0	0	0	1 (1)	0	1 (<1)	0
Vision blurred	0	0	0	0	1 (1)	0	1 (<1)	0
General disorders and administration site conditions	0	0	1 (1)	0	1 (1)	0	2 (1)	0
Fatigue	0	0	1 (1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0
Infections and infestations	0	0	1 (1)	0	0	0	1 (<1)	0
Hepatitis A	0	0	1 (1)	0	0	0	1 (<1)	0
Metabolism and nutrition disorders	0	0	1 (1)	0	0	0	1 (<1)	0
Anorexia	0	0	1 (1)	0	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (1)	0	0	0	1 (<1)	0
Dyspnoea	0	0	1 (1)	0	0	0	1 (<1)	0
Social circumstances	0	0	1 (1)	0	1 (1)	0	2 (1)	0
Alcohol use	0	0	1 (1)	0	0	0	1 (<1)	0
Drug abuser	0	0	0	0	1 (1)	0	1 (<1)	0
Vascular disorders	0	0	0	0	1 (1)	0	1 (<1)	0
Hypertension	0	0	0	0	1 (1)	0	1 (<1)	0

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Appendix 2.7.4.3.8.3.2.

Phase I/IIa Studies.

Reviewer Comment. *Refer to Section 7.1.3.3 for a description of potentially clinically remarkable subjects and section 7.2.12 for additional safety information from selected Phase I studies.*

17 Healthy Subject Phase I/IIa Studies. The following outlines the incidence of ADOs among the 17 healthy-subject Phase I/IIa studies (275 paliperidone treated subjects and 222 subjects treated with other formulations or medications in the ITT population of these trials combined).

- 9% of subjects receiving a "high dose" level which corresponds to 3 and 6 mg dose-levels (out of N=200 receiving the high dose level)
- 1% of subjects receiving the "low" dose, corresponding to 9, 12xx? and 15 mg dose-levels (N=152)
- 1% of subjects receiving single doses of other Paliperidone formulations
- 2% of risperidone treated subjects
- No placebo subjects

Dystonia (n=7), anxiety (n=2) and akathisia (n=2) were ADOs that occurred in more than 1 subject who received Paliperidone. Each event resulting in ADOs in subjects receiving other non-OROS paliperidone formulations did not occur in more than 1 subject.

Schizophrenia Phase I/IIa Trials. The following summarizes ADOs in the 3 schizophrenia Phase I/IIa studies (out of 111 Paliperidone subjects, 34 immediate-release (IR) paliperidone subjects, and 55 risperidone subjects in the ITT population) placebo subjects:

- 1 (3%) of IR paliperidone treated subjects was an ADO
- 4% of the Paliperidone high dose (OROS) treated subjects which included AEs of agitation, akathisia, psychotic disorder and hypertension that led to the ADOs in these subjects.
- 7% of risperidone treated subjects

The above high-dose paliperidone and risperidone ADOs occurred among 4 subjects.

7 Other Phase I/IIa Trials. Reported ADOs were as follows:

- A total of 18 subjects (5% out of 400 total subjects) were ADOs in the 7 trials.
- 14 out of the above 18 ADOs occurred in subjects receiving IR or ER OROS Paliperidone and were primarily due to nervous system disorder AEs (most commonly EPS).
- Each of the following AEs resulted in ADOs in 1 paliperidone treated subject (IR or ER OROS): ECG abnormality, T-wave abnormality, orthostatic hypotension, hypotension and postural dizziness.

7.1.3.1 Overall profile of dropouts

See previous section on adverse dropouts.

7.1.3.2 Adverse events associated with dropouts

This topic was previously discussed in sections on SAEs and ADOs.

7.1.3.3 Other significant adverse events

Reviewer Comments on Identifying Potentially Clinically Remarkable Subjects
A description of individual subjects (SAEs, ADOs, clinically remarkable AEs, clinically remarkable outliers on clinical parameters or other clinically remarkable observations in a given subject) could generally not be found in most in-text subsections of the SCS with a few exceptions. The SCS had a section focusing on special search strategies to identify AEs of interest of which results are summarized in Section 7.1.4 of this review. The sponsor's subsection on special search strategies in the SCS (Section 2.1.6) focused primarily on enumerating AEs of interest (to provide the incidence for each group). A discussion of potentially remarkable individual subjects in each special safety topic was generally limited and often did not provide subject numbers. It was difficult to reconcile the summary tables in these sections and summary tables on the incidence of SAEs, ADOs (in section that focused on SAEs and ADOs) with line listings and narratives found in the appendices of the SCS, since subject numbers to match these tables could not be found and the number of subjects was large (given the patient population that is known to have greater morbidity than the general population). A listing of at least ADOs and SAEs corresponding to summary tables could not be found. Sections of the SCS focusing on the incidence of outliers on clinical parameters often provided a few

statements on the number of ADOs and/or SAEs (but subject numbers could not be found) or a summary statement about potentially remarkable subjects (but subject numbers could not be found). Line listings of SAEs and ADOs could be found in appendices of the SCS and were helpful (were organized by study and treatment groups), listings to match the summary tables, but due to reasons above, it was difficult to reconcile these line listings with various in-text key safety sections in the SCS.

In addition to the above difficulties in identifying clinically remarkable subjects (e.g. in in-text sections of the SCS), additional concerns with capturing potentially clinically remarkable subjects is discussed in Section 7.2.8 in this review (on "Quality and Completeness of Data").

Most clinically remarkable subject described in this review were either found by review of CSRs (which generally only briefly described some subjects and did not always provide subject numbers) or upon review of line listings (of SAEs, ADOs for primarily completed Phase III trials and OL trials in the integrated longterm safety dataset) that were provided in appendices of SCS and narratives (of SAEs and ADOs). This was conducted as an effort to find clinically remarkable drug-related findings that were either unexpected due to the severe nature of a given event or in the type of event that occurred (e.g. refer to Section 7.1.2 describing several individual subjects).

An effort has been made to present individual subjects found not only in the original submission but in the 120-Day SUR submission line listings of SAEs and ADOs, as specified below.

A. Orthostatic Hypotension

Studies 303, 304 and 305 had no SAEs or ADOs of orthostatic hypotension. However, the following subjects are examples of clinically remarkable events associated with orthostatic hypotension that were found in various sections of CSRs of these studies and are noted below:

- *Subject 300541 in the 12 mg Pal group in Study -304 had SAEs of hypotension and other related events of **syncope, pauses on holter monitor and bradycardia.** This subject also had the AE of **orthostatic hypotension** as previously described in this subsection.*
- *Subject 200014 in the 6 mg Pal group of Study -303 had **"postural hypotension"** on Days 3 and 43 and met outlier criteria on Day 43. He had a **"sudden fall (accidental)"** on Day 17 leading to injury (a wound on the right arm). He was a 46 year old man with no prior meidal history or concomitant medications described in the description of this subject found on page 122 of the CSR.*
- *Subject 500102 in Study 305 (in the 9 mg Pal group) met outlier criteria for orthostatic hypotension **who withdrew early due to "dizziness, nausea, amnesia, headache and tachycardia".** Subject 50124 also is described under events of somnolence who also had tachycardia ("pulse=100-160 on minor activity") who **met outlier criteria for orthostatic hypotension** among other AEs (nausea, headache and amnesia).*
- *Subject 5000630 in the 9 mg Pal group of Study -305 was previously described as having AEs, but was not described as having SAEs or AEs leading to an ADO. Yet this subject was reported to have **syncope and episodes of tachycardia on Days 4 and 5 of treatment**, as*

*well as **episodes of orthostatic hypotension prior to and during DB treatment**, while also receiving concomitant lorazepam during the study.*

Also, subject 502318 in the 3 mg Pal group in Study -305 was found in an in-text section of the SCS on the topic of potential proarrhtyhmic AEs who had AEs of hypotension and syncope (Preferred term which was reported verbatim as "swoon") that led to an ADO on Day 3 but was not considered as SAEs. It is not clear if this subject has orthastatic hypotension as well, but this subject had similar events prior to Pal treatment.

B. Tachycardia in the Absence of Orthostatic Hypotension and Vital Sign Effects

Current labeling for Ris® generally describes the safety signal of tachycardia as occurring in association with orthostatic hypotension under Precautions. A clear distinction between tachycardia (or increased heart rate) associated with orthostatic hypotension versus tachycardia (or increased heart rate) in the absence of concurrent orthostatic hypotension cannot be found in approved labeling for Ris® and is not clearly addressed in the sponsor's proposed labeling, in the opinion of the undersigned. Yet, there were SAEs and ADOs due to or associated with tachycardia (or increased heart rate). Also refer to sections of this review on vital sign and ECG results from the Phase III clinical trials showing increases in supine heart rate and other related findings.

The examples below were of subjects that were found in in-text safety sections of the CSR of Study -303 (starting on page 143 of the CSR) or upon review of narratives. A few subjects did not have SAEs but were ADOs who had tachycardia in the absence of orthostatic hypotension. The following key features are noted in these 5 Pal subjects who received 6, 9 or 12 mg/day of Pal (these were the dose-levels employed in Study 303):

- ***A number of subjects below were generally healthy, had an unremarkable past medical history (PMH) and no concomitant medications and were young adults (between 23 and 33 years old).***
- *All subjects developed an **increase in heart rate in supine heart rate or by ECG** compared to baseline (on vital sign and ECG assessments).*
- *All subjects were **not described as having orthostatic hypotension (either as an AE or based on vital signs).***
- ***Several** subjects had additional vital sing or ECG changes: **became hypertensive or showed increased blood pressure, along with increased heart rate** during Pal treatment compared to baseline vital sign values (and/or ventricular rate ECG values).*
- *At least one subject had a **decrease in blood pressure** and increased heart rate (subject 201805) during Pal treatment compared to baseline heart rate with a positive dechallenge on these parameters. A decrease in blood pressure in the absence of orthostatic hypotension is an unexpected event.*
- *Subjects **generally showed a resolution of vital sign changes upon dechallenge** (within days after Pal treatment cessation).*

- *Almost all subjects **were first reported with a vital sign event by Day 4 or 5 of treatment** (one subject had vital sign changes noted on Day 7). **See Section 7.1.9** for a discussion of **time-dependent increases in heart rate recorded by ECG at multiple time-points.***
- *Some subjects **were ADOs or had SAEs of tachycardia.***
- ***A few subjects also showed QTc prolongation** that were generally first observed **on Day 6 or 7.***
- *These subjects are described below (most of these subjects were found on pages 144-146 of the CSR of 303). First the subject is summarized and then a more detailed description follows the summary:*
  - *Subject 200973 (generally healthy, unremarkable PMH, no concomitant medications, diazepam 5 mg/day as rescue medication on Days 1-4) was a 28 year old male. On **Day 4 of 6 mg Pal** treatment this subject had the **SAE of sinus tachycardia** and **AEs of dyspnea, increased BP** (compared to baseline). Additionally **non-specific ST wave changes (NSST)** were found on ECG that were absent upon a repeat ECG (on Day 4). While this subject had intermittent NSST wave changes, first observed at baseline, the timing of the adverse events (on Day 4) are probably drug-related in that Pal-induced tachycardia may have triggered an increase in BP to maintain cardiac output and this subject appeared to be at risk of angina given the AE of dyspnea and NSST wave changes associated with these events.*
    *The following provides more details on subject 200973. He was reported as an **ADO on Day 4** (in the **6 mg Pal group**) due to **sinus tachycardia that** was also reported **as an SAE.** The subject also had **"breathlessness," "palpitations," and increased BP** (130/40 compared to 118/80 at baseline) **on Day 4** (according to the narrative). Heart rate on Day 4 was 140 bpm (per ECG) compared to 74 bpm (per ECG) at baseline (the 4 and 10 hour post-dose ECGs showed increased heart rates). Sinus tachycardia was reported as an SAE on Day 4 due to prolonged hospitalization. The subject was monitored in an intensive care unit for 2 days and was treated with a 10 mg dose of propanalol. Pal was also discontinued on Day 4. In addition to the above events, **intermittent non-specific T (NSST)-wave abnormalities** were revealed at baseline and on the first scheduled (on-treatment) ECG assessment at 4 hours post-dose of Pal **on Day 4**, but were not observed in **a repeat Day 4 ECG (sinus tachycardia with normal repolarization)**. On Day 11 (7 days post-treatment) ECG heart rate was 57 bpm. Blood pressure values were not found in the CSR-in-text description and the subject was not reported as having AEs associated with abnormal BP. Vital sign values returned to normal after discontinuing Pal treatment.*
  - *Subject 200974 was a 49 year old male subject (generally healthy, unremarkable PMH and no concomitant medications) in the **9 mg Pal group** who was reported as an **ADO** due to **"bundle branch block left, sinus tachycardia."***

In summary, while this subject may have had a pre-existing cardiac condition (as may be suggested by his baseline ECG repolarization findings), the timing of the heart rate and blood pressure changes during treatment (on Day 4) and resolution of these changes which occurred upon dechallenge (see more details below) is suspicious of Pal-induced effects on vital signs.

The following provides details on vital sign changes observed in this subject: ***increased BP and HR*** *first reported* ***on Day 4*** *(110 bpm supine, 120 bpm standing and ECG ventricular rate of* ***125 bpm at 4 hours post-dose compared to 73 bpm (per ECG) at baseline.*** *His heart rate* ***approached baseline values on Day 8 (4 days after cessation of 9 mg/day of Pal). His blood pressure was only 92/70 mmHg (supine) and 110/70 (standing) on Day 8 (heart rate was 90 bpm).***

This subject had ***left anterior fascicular block on ECG at baseline****, during treatment and at post-treatment. This ECG finding was probably not drug-related.*

- *Subject 201022 (generally healthy, unremarkable PMC and no concomitant medications) was in the 12 mg Pal group (45 year old male). The subject was reported as an* ***ADO of "dyspepsia, tachycardia (twice), electrocardiogram QT interval prolonged, blood pressure increased." Pal was stopped on Day 7 (Day 4 Pal treatment was held for that day due to "QT interval prolonged.".*** *Reported* ***SAEs included increased blood pressure, tachycardia and prolonged QT interval (according to the narrative).***

While undiagnosed underlying cardiovascular pathology appears to have existed in this subject, a role of Pal is suspected in exacerbating an underlying hypertension by inducing increased heart rate and possibly by a small unremarkable QT prolongation effect and given the timing of the events (see more details in the next paragraph). It is not clear if this subject had angina since ECG assessment results could not found in the narrative or CSR description of this subject on Day 2 when he had dyspepsia. This subject was eventually treated with ranitidine (after Pal treatment was discontinued) suggesting that the clinician treating this subject considered the adverse event to be unrelated to the cardiovascular related events.

The following provides more details on this subject. On Day 2 he has "mild dyspepsia" ("burning in chest-verbatim"). ECG and vital sign measures could not be found in the narrative for Day 2 despite that angina can present clinically with the complaint of this nature (e.g. dyspepsia, indigestion). ***Increased heart rate and blood pressure*** *were* ***first noted on Day 4,*** *as well as the* ***SAE of "prolonged QTc interval) on Day 4 (QTcB of 468 msec compared to 396 msec on per-dose Day 1 ECG, QTcF=419 msec).*** *The subject* ***complained of palpitations*** *and* ***heart rate increased to 124 bpm compared to 71 at baseline*** *and* ***supine BP increased to 180/114 mmHg*** *(standing was 170/110 mmHg)* ***compared to supine BP of 134/90 mmHg at baseline*** *(130/90 standing).* ***At 9-days (Day 16) after discontinuing pal treatment HR and BP returned to baseline values*** *(supine BP was 130/90 and HR was normal). QTcF, QTc sagie derived or linear derived values were not provided in the description of this subject on page 145 of the CSR, but the narrative had QTcF value of 419 msec on Day 4. QTcB changes were probably an over representation of potential QT prolongation effects since heart rate was increased (such that QTcB values would be expected to be falsely high). It was believed by the "local cardiologist" that the patient had "essential hypertension" and that he had ECG findings revealing "concentric left ventricular hypertrophy." BP on Day 16 (9 days post-dose) had decreased to 130/90 mmHg and HR was normal and with treatment (enalapril) BP ranged from 120-126/80-84 on Days 23.*

- *Subject 201102 was a **12 mg Pal subject** (a 23 year old male with no cardiac-related history) in Study 303 **did not have any SAEs reported** but was reported as an **ADO due to "ECG specific abnormal"** (QTcB ≥ 500 msec **on Day 6**, as well as **increased QTcF, QTLc and QTcLD of up to approximately 450 msec).***

In summary this was a young male with an unremarkable PMH who developed increases in BP and HR by Day 5. QTc prolongation (including QTcF of 454 msec) was also observed. The increases in heart rate, QTc and possibly increased BP appeared to be Pal related. While evidence for a viral illness with one day of fever (Day 5) may have played a role in the HR and BP changes, a positive rechallenge on HR was observed and is strong evidence for a Pal induced effect. Since BP values were not found in the narrative or CSR descriptions, after Day 5 (that included days during rechallenge and dechallenge of Pal treatment) it is difficult to assess the role of Pal on BP. However, in the absence of this information a Pal induced effect or role of Pal in increased BP is considered to be likely. QTc increases relative to BL values that resolved upon dechallenge is also strong evidence for a Pal effect. Although successive ECGs were obtained during the rechallenge of Pal treatment, it is difficult to interpret QTc results in reference to the rechallenge dose that was given for reasons described below.

*The following are more details on the this subject. The CSR (on page 155 in another section of the CSR that focuses on QT interval results) as indicated an **over 60 msec prolongation of QTcLD on Day 6** compared to the baseline value (pre-treatment average value). This subject was also described in more detail on page 156-7 of the CSR as also developing **increased HR and increased BP first noted on Day 5** of treatment **(130 bpm HR and 140/90 mmHg BP at supine, 140 bpm HR and 142/90 mmHg at standing compared to baseline values of 77bpm and 120/84 BP at supine and 90 bpm HR and 122/84 mmHg at standing).** "No ECG was available" when these vital signs were obtained on Day 5. However, on Day 6 an ECG showed QTc prolongation (for any QTc method employed) from **approximately 370 to 375 msec (pre-treatment average) for QTcF, QTlc and QTcLD to approximately 440 to 450 msec for QTc F, QTlc, and QTcLD at 4 hours post-dose on Day 6. QTcB** at this time-point was **505 msec compared to 387 msec at pre-treatment** (given increased HR this value is considered an over-exaggerated estimate of the actual magnitude of QT interval prolongation). **QTc interval values (for all QTc methods) returned to baseline** values **on the ninth day (Day 16 of the study) after stopping Pal treatment and HR was only 67 bpm (near baseline values).** BP values could not be found in the sponsor's description in the CSR on page 157.*

The following additional information was found in the narrative of this subject. This subject also had fever on Day 5 with tremor (hands), and glossitis and baseline CBC showed elevated lymphocytes, "decreased" neutrophils and elevated glucose. While tachycardia was first observed on Day 5 in "sinus tachycardia" was observed several days after resolution of the fever (resolved in 1 day). Furthermore, according to the narrative Pal was held on Day 6 and resumed on Day 7 while HR was 140 bpm on Day 5, then 115 bpm on Day 6, and then increased again on Day 7 to 144 bpm (Day 6 and 7 values were obtained by ECG). Therefore, a positive rechallenge on tachycardia was observed in this subject. Blood pressure values for these days (Days 6

and 7 or thereafter) could not be found in the CSR description or the narrative of this subject. Results of QTcF over Days 6 and 7 are more difficult to interpret in determining if there is a positive rechallenge effect since QTc Pal effects appear to be greatest near approximately 22 hours post-dose (near Tmax) and since the exact timing of ECG assessments relative to dosing on these days could not be found in the CSR and narrative descriptions.

- *Subject 201805 in Study -303 (a 33 year old male with an unremarkable PMH, no concomitant medications but "remarkable" ALT elevation and triglyceride elevation at baseline) had 12 mg daily Pal treatment* ***discontinued on Day 7 (ADO) who had an SAE of tachycardia*** *that was* ***first noted on Day 4.*** *This subject also had* ***hypotension*** *on Day 4.*

  Given the timing of the vital sign events of hypotension and tachycardia relative to treatment, along with a positive dechallenge that was observed, these events are likely to be Pal related (see details below).

  The following are more details. On Day 4 ***HR reached to 120 bpm supine (124 bpm standing) compared to 71 bpm (per ECG) at baseline (84 bpm supine at baseline).*** *The subject also developed* ***"hypotension"*** *in which* ***Day 4 BP was 100/65 mmHg, supine (115/75 standing) compared to 135/65 mmHg, supine at baseline*** *and* ***decreased further to 85/55 mmHg, supine, on Day 6*** *(80/50 standing). According to the narrative, the* ***"hypotension was reported on Day 5." "Paliperidone was discontinued and blood pressure normalized the following day."*** *Supine BP of 115/80 mmHg and HR of 93 bpm were observed on day 7. The tachycardia prolonged his hospitalization. Tachycardia was reported to resolve by 12 days and hypotension by 3 days without treatment. ALT was reported to be "increased" during the study.*
- *Subject 201803 in Study -303 (33 year old male) had a* ***SAE of tachycardia*** *with increased heart rate* ***first noted on Day 7 of 6 mg daily of Pal treatment compared to baseline*** *values while BP generally did not change from baseline vales. This subject* ***was not described as having orthostatic hypotension*** *(on page 146 of the CSR). His* ***baseline supine and standing HRs were 72 and 76 bpm, respectively compared to supine and standing HRs of 106 and 130, respectively on Day 8 of treatment. Metoprolol treatment was started on Day 10 and given for 11 days.*** *Tachycardia resolved by 14 days. Paliperidone treatment was over 21 days, then the subject withdrew from the study on Day 22 "due to consent withdrawn" with an ECG HR of 73 bpm on that day.*

Tachycardia occurred after some subjects in the longterm OL trials as well. The following are some subjects found in the 120-Day SUR Submission:

- *Subject 200303: This subject was a* ***generally healthy 37 year old male (unremarkable PMH)*** *subject in OP Study -703 who* ***previously received DB olanzapine (in the 6-week lead-in Study*** *-303) who developed* ***tachycardia*** *initially reported as an AE* ***while receiving 9 mg daily*** *on Days 1-3 which was then decreased to 3 mg daily on Day 4.* ***On Day 5 tachycardia*** *was reported* ***as an SAE*** *and the subject* ***was hospitalized (HR was 140 bpm). Study drug was temporarily discontinued*** *and* ***resumed on Day 7 at the 3 mg daily*** *dose-level. Orthostatic hypotension was not described. No other clinically-related information*

could be found in the narrative. However this subject developed intermittent episodes of "acute paranoia" that lead to gradual increases of Pal and temporary resolution of the paranoia. The narrative does not a recurrence of tachycardia associated with subsequent increases in the Pal dose.

A discussion of vital sign or ECG changes that were observed after subjects were switched from DB Olanzapine (10 mg/day) to OL pal is provided in sections on vital sign and ECG changes in this review.

The following describes in more detail the changes in the dose after resuming Pal treatment and additional information. The tachycardia resolved after 13 days at this low dose-level but the patient developed "acute paranoia" and was hospitalized. He was receiving diazepam intermittently during the study. After resuming the dose at 3 mg daily on Day 7, the dose was increased to a daily dose of 6 mg (on Day 30) due to paranoia, and to 6 mg on Day 34 with resolution of acute paranoia until Day 64 upon which the subject was hospitalized for "acute paranoid ideas." The daily dose was increased to 12 mg on Days 71-74 and decreased again to 9 mg. It is not clear why the dose was decreased. However, the subject received 9 mg daily on Days 75-79 until he withdrew consent on Day 79.

- *Subject 500603: This subject was a generally healthy 18 year old (Malaysian) with an unremarkable PMH and taking no concomitant medications who developed an* ***SAE of tachycardia on Day 4 of OL 9 mg daily of Pal in Study -705 that persisted with an abnormal ECG of NST-wave abnormalities and "sinus tachycardia at 106 bpm," noted on Day 15. He was not hospitalized but also had "inability to walk for a distance or to exert himself in view of breathlessness and lethargy." Ultimately this subject was reported as an ADO on Day 22 due to these AEs.*** *Dyspnea was first reported on Day 13 and the "cardiology interpretation stated that the precordial leads on the Day 15 ECG were not valid." There is no mention of a repeat ECG on this study day, but an ECG on Day 22 was "within normal limits." This subject also reportedly received 9 mg daily of DB Pal in a 6-week lead-in Study that lead to early discontinuation on Day 23 due to "lack of efficacy." The narrative did not provide an vital sign information during this initial Pal exposure.*
- *Subject 200601: This* ***30 year old male subject*** *had a* ***history of hypertension and tachycardia but no concomitant antihypertensive agents*** *or other medications. He* ***developed transient tachycardia*** *early* ***during DB olanzapine*** *treatment in the lead-in 6-week study (****on Days 4-6*** *of DB treatment).* ***These events reappeared on Day 6 of OL Pal (at 9 mg/day) with a HR of 150 bpm (reported as an SAE) and BP of 170/100 which led to an ADO on Day 7. The events resolved by Days 8 or 9 without treatment.*** *This subject also had psychotic-related AEs, as well as a potential underlying condition (history of tachycardia and hypertension) that may have contributed to the degree of cardiovascular changes this subject. It is possible that this patient's history of tachycardia and hypertension were associated with past treatment with antipsychotic medications (but this is speculation), since it appears that he did not require antihypertensive treatment and the narrative did not describe abnormal vital signs at screening or at baseline. Furthermore, the AEs of high BP and HR resolved upon dechallenge of Pal treatment. Consequently, the AEs in this subject are likely to at least, in part, be related to antipsychotic drug treatment.*

Tachycardia in Phase I Subjects and Potential Food Effects.

Additional subjects were found to have tachycardia (in which orthostatic hypotension was not reported) and dyspnea among young Phase I male subjects. These events occurred after these subjects were given their first and only SD of 15 mg Pal after a high fat meal (that occurred on the next day after treatment). This was the first and last dose given to these subjects, since they were also ADOs. A subsection E below describes these subjects (see the subsection entitled "Potential Food Effects on Cardiovascular and Respiratory Related Events in Phase I trials"). Also refer to Seciton 7.1.12 C for related safety results from 2 Phase I food effect studies using SDs of 12 mg or 15 mg of the Phases III, [redacted] formulations.

Increased BP

Some of the previously described subjects had events that included increased blood pressure. The following subjects were in the "prevention relapse" Study -301 and were found as examples of additional examples of subjects with potentially clinically noteworthy increases in BP (found in the 120-Day SUR, as this study was completed after N000 and before this SUR):

- *Subject 100121 (**ADO due to "blood pressure increased"**) had a progressive increase of blood pressure during Pal treatment that did not resolve with the addition of clonidine to his usual pre-study, antihypertensive regimen of benazepril HCl. Pal at the 9 mg daily dose level was discontinued after 21 days of treatment (Day 21 of the run-in phase) due to "elevated blood pressure which was persisting." This subject had a history of hypertension that was being treated with benazepril HCl that appeared to well controlled given his baseline vital sign values obtained (124/72 mmHg at standing). A progressive increase in standing BP (of up to 140/84) was observed despite the addition of clonidine treatment and despite multiple increases in the dose. A role of Pal in inducing poorly controlled hypertension is suspected on the basis of the narrative information found on this subject.*

Refer to the last section of this review for further comment and recommendations regarding hemodynamic drug effects and potential drug effects.

C. Cardiovascular Related Events Associated with Syncope

The following are examples of subjects with syncope who also had clinically remarkable vital sign or ECG related events or other clinically remarkable events. Syncope was sometimes associated with known drug effects, such as orthostatic hypotension but also included cases of potentially unexpected drug related adverse effects, such as the possibility of sinus pause.

The following subject was found in an in-text section of a CSR of one of the Phase III trials: ***Subject 300541: "Pauses" of up to 8 seconds on holt monitoring of S300541.*** *This subject had* ***SAEs of "hypotension"*** *(110/72 mmHg at supine) and* ***"dizziness."*** *This subject also developed* ***"syncope"*** *which was reported as an AE. A description of his syncope cannot be found in the narrative or in-text CSR description of this subject. This subject also had* ***bradycardia*** *(40 bpm at supine, 38 bpm at standing) and met outlier criteria for orthostatic hypotension. EKG showed* ***a possible lateral infarct of undetermined age, left anterior fascicular block and heart rate of 67 bpm,*** *while cardiac enzyme levels were normal. Holter monitoring revealed "several pauses" lasting up to 8 seconds. These events occurred early in Pal treatment (Days 5 and/or 6*

of 12 mg daily treatment) near the time when peak cardiovascular drug effects were revealed by descriptive statistical results of vital sign and ECG data by treatment group, as described later in this review. The subject was withdrawn from the study on Day 6, but it is reported that the reason was due to "exacerbation of schizophrenia." Yet, cardiovascular events and SAEs occurred on Days 5 and 6 and were assessed by the investigator as being "possibly" drug-related. These cardiovascular adverse events also resolved within 2 to 4 days after treatment cessation, which is strongly suggestive of drug-related events. This subject was ***not described as having any pre-existing conditions or concomitant medications*** *that could potentially account for these events. However, the subject was male and 50 years old which are risk factors for cardiovascular disease.*

The following description of Subject 300541 was found in the narrative on pages 2555-6 of an appendix of the SCS:

[redacted]

Appears This Way
On Original

Subject 300541 (paliperidone, preferred term: dizziness, hypotension, syncope, psychotic disorder, bradycardia (twice); [redacted] was a 50-year-old white man with a diagnosis of paranoid schizophrenia. The medical history included asthma, intermittent headaches, agitation, and insomnia. The physical examination at screening was normal. There was no relevant history of bradycardia, dizziness, or syncope.

Laboratory values at screening showed elevated alanine aminotransferase, aspartate aminotransferase, C-peptide, and gamma-glutamyl transferase. The subject discontinued aripiprazole and lithium carbonate on Day -5. Lorazepam 1 to 7 mg "as needed" was given daily between Day –5 and Day 4. Concomitant medications at baseline were benzatropine mesylate 1 mg twice daily, salbutamol inhaler, and rofecoxib 25 mg/day.

On screening Day –4, the ECG, reported as abnormal but not clinically important, showed left anterior fascicular block and a heart rate of 76 beats per minute (bpm). Blood pressure on screening Day –6 was 124/78 mmHg (standing) and 122/76 mmHg (supine); his pulse rate was 92 bpm (standing) and 90 bpm (supine). His weight was 131.5 kg (body mass index 39.3 kg/m^2).

On Day 5, while receiving paliperidone 12 mg/day, the subject experienced the serious adverse events of *dizziness* (dizziness-verbatim) and *hypotension* (hypotension-verbatim) and non-serious adverse events of *syncope* (syncope-verbatim) and *psychotic disorder* (exacerbation of psychosis-verbatim). No vital signs information is available for this day. Study medication was stopped on Day 5 as a result of the exacerbation of psychosis (requiring too much lorazepam: CIOMS); treatment with lithium 300 mg twice daily was initiated on Day 6 and aripiprazole 15 mg b.i.d. on Day 7. The subject was withdrawn from the study on Day 6 due to the adverse event "exacerbation of psychosis".

On Day 6, serious adverse events of *bradycardia* (bradycardia-verbatim) and *heart rate irregular* (delay in pulse-verbatim) were reported. He was hospitalized due to a standing pulse rate of 38 bpm (40 bpm supine); his supine

and standing blood pressures were 110/72 mmHg and 112/72 mmHg, respectively. An ECG obtained on Day 5 showed normal sinus rhythm, left anterior fascicular block, and a possible lateral infarct of undetermined age, with a ventricular rate of 67 beats per minute. His cardiac isoenzymes were reported as normal. A Holter monitor demonstrated several pauses including one 8-second pause. A computed tomography scan of the head revealed no acute intracranial process and no bleed (source: CIOMS). A cardiology consultation was requested but the subject eloped before he could be evaluated (source: SAE follow-up forms). The dizziness, hypotension and syncope resolved in 2 days, the exacerbation of psychosis resolved in 13 days, and the bradycardia and delay in pulse resolved in 4 days.

The investigator assessed the serious adverse events "dizziness" and "hypotension" to be moderate in severity and possibly related to the study medication. The "exacerbation of psychosis" was rated mild and not related to study medication, the "syncope" mild and possibly related, while the serious adverse events "bradycardia" and "delay in pulse" were considered severe and possibly related to the study medication.

In many instances it is difficult to differentiate adverse events from preexisting disorders. Even though there were ECG abnormalities at baseline, the subject had no prior symptoms of bradycardia, dizziness, or syncope. Dizziness, hypotension and psychosis have been reported with the use of paliperidone, although these events could also be due to the subject's underlying condition including heart block which may signal underlying cardiac disorders. This subject received 5 doses of 12 mg paliperidone; no rechallenge was performed. Therefore a causal relationship between the adverse events "syncope" and "exacerbation of psychosis" and the serious adverse events "dizziness" and "hypotension" and the intake of paliperidone is difficult to assess, but not totally excludable.

Bradycardia and delay in pulse have also been reported with the use of paliperidone. These serious adverse events occurred at the same time the study medication was stopped, the sponsor considered that a causal relationship between the serious adverse events "bradycardia" and "delay in pulse" and the use of paliperidone could not be excluded.

(Manufacturer's Control No.: US-JNJFOC-20040900273(5)).

This subject is listed in a listing of subjects meeting outlier criteria on page 308 of a 475 page table in an appendix of the SCS on page 4350 (which is page 308 of the 475 page table) and listed as having:

- *Standing and supine HRs of 38 and 40 bpm, respectively on Day 6 of the study*
- *Compared to standing and supine heart rates of 80-92 and 90-76 bpm, respectively on previous assessments (includes: 2 baseline assessments and assessments on Days 2, 3, and 4).*

Additional Reviewer comments on the above subject: Sinus pauses (and bradycardia and hypotension) have been previously reported for at least a related drug, olanzapine (following IM treatment in 2 subjects and oral olanzapine in 1 subject as described in approved labeling, in 2 Phase I trials of normal healthy subjects in which telemetry monitoring was employed). It is notable that these types of events may have occurred in this subject at a time-point when plasma levels were dramatically rising or near Tmax. Another concern is that drug levels of Pal can be dramatically affected by food intake, among other potential factors that may impact on PK of Pal. However other factors, aside from PK factors, that may influence cardiovascular drug effects need to be considered that may at least playing a role. That is, drug effects on the cardiovascular system are not likely to be solely dependent on drug level or to be static effects. Instead, drug effects may be strongly influenced by non-drug-related dynamic physiological changes in the cardiovascular system in the healthy patient, as well as in the patient with pre-

existing cardiovascular conditions (e.g. consider diurnal fluctuations in the cardiovascular system, consider a patient with an already compromised cardiac output who then develops drug-induced tachycardia that may lower cardiac output further and trigger hypertensive compensatory episodes or hypotensive episodes, among other considerations). An apparent time-dependent (which could be related to either PK factors and/or physiological dynamic related factors) was observed in cardiovascular related clinical parameters as described later in this review. Furthermore, some of these effects appeared to be dose-dependent (see results on vital signs and ECGs in this review).

Refer to the final section of this review for further comment and recommendations. .

The following subject was in an OL trial and was reported in a safety alert report under the Paliperidone IND (ER OROS) is described below because the subject was a young generally healthy female who died suddenly without having any known non-drug-related reason to explain her death.

A Summary of Events and Death in Subject [redacted] based on information from a Safety Alert Report under IND658850.

A sudden death associated with syncope and possible seizure after at least 3 months of OL Pal treatment (12 mg/day) in Study -701 *was reported in a Safety Alert Report under the Paliperidone IND (IND 65850 for the OROS Pal formulation, a N184 4/3/06 submission). See a description of this subject below. The following are reviewer comments about this subject. In the opinion of the undersigned reviewer the events leading to death were likely to be related to the study drug, since the subject was healthy, and was only receiving trihexyphenidyl as needed, was a nonsmoker and was not described as having pre-existing conditions or abnormalities or risk factors to explain the cause of sudden death. Clinical data on this subject are limited, but the clinical presentation (in the absence of other clear causes) is highly suggestive of a Pal related adverse events that led to death. Possible diagnostic considerations are the following: pulmonary embolism versus cardiorespiratory arrest secondary to an arrhythmia, versus aspiration of emesis and bronchospasm, together with slightly low potassium and sodium levels, among other cardiac and/or CNS related events that may lead to sudden death. While the subject could have had a dystonic reaction leading to compromise to her airway, she scored 0 on SAS and BARS at her last study visit approximately one month before the day of her death. It is not clear why she was given trihexyphenidyl (perhaps it was being used off-label for agitation, but this is only speculative).*

The following is a more detailed description of events that ensued in subject [redacted] based on information in the safety alert report. The subject had schizophrenia who suddenly died after over 3 months of receiving 12 mg daily of OROS Pal in the OL extension trial -701 (which followed a "prevention of recurrence" trial, Study -301). She was last assessed in the OL study on 12/7/05 and was not exhibiting acute psychotic features, was sleeping and eating well, and had normal vital signs and a negative urine pregnancy test. The mother of the patient was contacted about changing the date of her next study visit (scheduled for [redacted], but the mother could not change the date). On [redacted] the patient was noted by the mother to

*become **"very anxious, agitated and complained of breathlessness."** The mother **gave her a 2 mg trihexyphenidyl tablet**, according to instructions. No other information could be found as to why this concomitant medication was prescribed and her AIMS, SAS and BARS scores were all 0 at her last study visit within the previous month (on 12/7/05). "Within some time" after receiving this drug the subject **"started vomiting" then, "within no time"** the subject was reported to have **"severe convulsive movements of the entire body" and became "unconsciousness."** She was **evaluated at a hospital at approximately** [redacted] **that day and was observed** over approximately **3 hours before being transported (while "deteriorating") to another hospital but the patient died in transit. During the 3 hours during hospitalization** the internist found her in a **"stuperous" state, unresponsive to pain, while DTRs were "present."** Her **blood pressure was "reported to gradually fall"** (vital sign measures could not be found). An ECG and EEG were not performed. Laboratory values were as follows: glucose was normal, **potassium was low at 3.1 (NR 3.5-5.2 mM), sodium was low at 126 (NR: 134-145 mM).** No other assessments could be found in the safety alert report submission. The patient is "presumed" to have not undergone an autopsy. **The differential diagnoses by the investigator included: convulsion, bronchospasm and respiratory failure, rule out pulmonary embolism. The treating physician in the patients home town did not suspect drug overdose, poisoning (did not have any "signs or symptoms" of poisoning) and "his clinical diagnosis was: posticital stupor/postictal coma."***

Additional cases of syncope were found by the undersigned reviewer that were not reported as SAEs (as specified below) that strongly suggest Pal induced effects:

- **Copied from the narrative found in the 120-Day SUR**
  Subject 100140 (paliperidone dosage at onset of event: 12 mg/day; syncope; [redacted] was a 27-year-old white man with a diagnosis of paranoid schizophrenia. At screening, the subject's medical history noted 4 prior hospitalizations for psychosis. During the double-blind study, the subject received placebo for 12 days before entering the open-label study. Adverse events reported during the double-blind study were "aggression" and "exacerbation of symptoms (increase in psychosis)." During double-blind, the subject received lorazepam as a rescue medication. During the open-label study, the subject received paliperidone 12 mg/day for 65 days. On open-label Day 1, the subject's blood pressure was 118/74 mmHg, with a pulse rate of 70 beats per minute (bpm); vital signs were stable throughout the study. On open-label Day 65, the serious adverse event "syncope" was reported when the subject fainted while on a trip with his group home. He was admitted to the hospital for observation with a diagnosis of syncope. Paliperidone was discontinued at that time. A cardiac evaluation was performed on an unspecified date but the results were still pending. The syncope resolved in 7 days and was considered by the investigator to be severe and possibly related to study medication. On Day 67, the subject was withdrawn from the study due to the serious adverse event. (Manufacturer's Control No. US-JNJFOC-20050802498(2)
- *Subject 500630: The following subject did not have SAEs and was not an ADO but is described here in this review, because the subject had **syncope** associated with*

***tachycardia** and **orthostatic hypotension** which were reported as AEs. Subject 500630 (30 year old female) in the 9 mg Pal group of Study 305 had the AE of syncope (verbatim term: "fainting attack" considered to be mild on Day 4 (this was not an SAE). This subject also had episodes of orthostatic hypotension (met outlier criteria including assessments prior to the DB phase) and was receiving concomitant lorazepam (1 to 6 mg po daily). This subject had episodes of tachycardia on Days 4 and 5 of DB treatment (returned to normal on Day 8). Sinus tachycardia revealed by ECG assessments on Days 4 and 5 was considered "clinically significant." However, subsequent ECG assessments were interpreted as normal and the subject completed the study on Day 44 without requiring treatment for her AEs.*

The timing and nature of these events (early in the first week of treatment) is generally consistent with results showing Pal effects on cardiovascular related clinical parameters described later in this review.

- *Subject 500407 (55 year old male) in the 15 mg Pal group of Study 305 did not have an SAE or AEs leading to an ADO but is described here due to an AE of **"syncope"** on Day 34 (of moderate severity, "resolved in 1 day") and **borderline QTc interval values** during ECG assessments on Day 4 (10 hours post-dose time-point), Day 7 (22 hours post-dose time-point), Day 35 (1-2 hours post-dose) and Day 42. None of the QTc values reached 450 msec or greater and the subject completed the study on Day 42. The timing and nature of these events is generally consistent with results on Pal effects on related clinical parameters described later in this review.*
- *Subject 502318 in Study -305 had AEs of **hypotension and syncope** (Preferred term which was reported verbatim as "swoon") that led to an ADO on Day 3 and that spontaneously resolved within several days after treatment cessation. These events were not considered as SAEs. This subject had similar events at baseline, suggesting that the events could be at least partly related to a pre-existing condition.*

A search for AEs of syncope among the narrative section (an appendix) of the SCS for SAEs and ADOs revealed additional subjects with SAEs or AEs due to an ADO of syncope, that were not found elsewhere in in-text sections of the SCS (as described in this review). The following were 2 notable events given the nature of the events and that alternative non-drug-related explanations for these events could not be found or described in the narratives or CIOMS forms found on these subjects:

- *Patient number 103772/1000140: this subject was a healthy 28 year old male with schizophrenia in the OL Study -701 who had no concomitant medications and had **syncope after approximately 2 months of 12 mg Pal daily.** This event led to hospitalization. A "cardiac work-up" was conducted and "resulting are pending." There was no additional information that could be found this subject (information was found in a CIOMS report, since this event occurred past a May 31, 2005 cut-off deadline in this ongoing trial.*
- *Subject 700015 in a Phase I study (-P01-1007) who had **syncope for 60 seconds** that occurred upon standing after 3 hours and 48 minutes after receiving 1 mg IR Pal. This 52 year old healthy woman (with an unremarkable past history and no*

concomitant medications described in the narrative) continued to have "extreme dizziness" and nausea for 4 hours post treatment. She was able to continue the remaining 4 treatment conditions in this Phase I study without recurrence of syncope or orthostatic hypotension. One possible consideration is that Phase I trials generally involve

Additional SAEs and/or ADOs of syncope found in the 120-Day SUR and/or in OL Trials

- *Subject 200986: this subject was previously described who had a 5 minute episode of loss of consciousness (**grand mal convulsion reported as an SAE and lead to an ADO**) that was not followed by a post-ictal state of which **it is not clear if whether or not this subject had a seizure versus another type of syncopal event**. Information on the subject is limited. This subject is described in more detail under the subsection on seizures below (subsection I).*

Response to an Inquiry of Any Cases of Syncope

Since a description of subject 300541 (with sinus pauses) and others could not be found in the in-text sections of the SCS in the submission, including a section that focused on events of syncope and other potentially pro-arrthmic-related events, the sponsor was asked to provide listings and narratives of subjects with symptomatic bradycardia, tachycardia, hypotension, orthostatic hypotension or syncope (who were asymptomatic at baseline) using their November 1, 2005 cut-off date (since this was the cut-off date for the original submission).

A response to this inquiry was recently received, but since it was received late in the review cycle (N006, 6/27/06) then results will be described in an amendment review or in a review of a response to an approvable action (if the Agency takes an approvable action on this NDA).

Also see related subsections below on Seizures, Dizziness and ischemia-related events, as well as the previous subsection for potentially related events..

D. Dizziness

2 ADOs due to dizziness occurred in Study 305 (500102 and 5011244 in the 9 mg and 15 mg pal groups respectively), as described below.

- *Subject 501244 in the **15 mg Pal group** of Study 305 was an obese 41 year old male with **"fuzzy thinking," dyspnea and dizziness the led to treatment cessation on Day** 7. Vital signs were normal on Day 7.*
- *Subject 500102 in the **9 mg Pal group** in Study 305 **withdrew early due to "dizziness, nausea, amnesia, headache and tachycardia" with tachycardia reported as an SAE.** This subject also had mild somnolence as an AE. **Tachycardia was described as a"pulse=100-160 on minor activity."** This subject also **met outlier criteria for orthostatic hypotension.***

See previously described subjects with seizures and syncopal episodes (or in some cases appeared to be near-syncopal episodes based on the verbatim term provided).

The CSR of Study 303 indicates that there were no SAEs due to dizziness but:

- *One **ADO occurred in a 12 mg treated subject due to "dizziness" on Day 29** (subject 201526). This subject had **dizziness and epigastric abdominal pain starting on day 15** and was also reported to have **AEs of "first degree AV block" and "blurred vision."** It is not clear if angina was ruled out and if there were other non-drug-related causal factors that existed in this subject.*

E. Potential Food Effects on Cardiovascular and Respiratory Related Events in Phase I Subjects

*While the focus of this section of the review is primarily on Phase III trials, it is important to consider the remarkable food effect observed with Pal (based on Phase I studies, as previously described in this review). Upon review of line-listings of SAEs and ADOs of Phase I trials and review of selected narratives the following subjects were found as having **ADOs of dyspnea and tachycardia (2 subjects) or postural hypotenision and dizziness (in 1 subject)** that were also associated with other AEs as described below. These subjects were in the food effect Study – P01-1008 which used the 15 mg SD level of Pal in a crossover study design. While there were no SAEs reported in this study, one caveat to consider is that Phase I trials are generally conducted on-site (not as outpatients). Consequently if an AE that may have resulted in hospitalization and therefore would be reported as an SAE in an outpatient study may not necessarily be reported in an inpatient study setting (such as the setting of most Phase I trials). The following describes the ADOs with cardiovascular related events:*

- *Subject 100813 was a 29 year old generally healthy male who was reported as an **ADO due to sinus tachycardia in the morning of Day 2 of Period 1 following 15 mg Pal** given **after ingestion of a high-fat breakfast.** **Dyspnea** was reported by the subject 4 hours later which was treated with oxygen (4 L/min). Both events resolved within 30 and 17 hours, respectively. This subject developed additional AEs on the evening before Day 2: "moderate anxiety" that was treated with 5 mg diazepam PRN, "mild impaired concentration," "mild diarrhea," and "mild dry mouth."*
- *Subject 100824: was a 27 year old generally healthy male who was reported as an **ADO due to dizziness** at the same time of the onset of events in the subject described above (subject 100813) which was **in the morning of Day 2 of Period 1 after 15 mg Pal given in the fed state** (as with the previously described subject). The subject had an episode of **orthostatic hypotension** approximately 3.5 hours prior to the dizziness. The dizziness was treated with oxygen (4 L/min). This subject also had **chest pain** (an ECG result cannot be found in the narrative), as well as **abnormal vision** (mild intensity) and abdominal pain (the latter was treated with diazepam 5 mg PRN).*
- *Subject 100811 was a 19 year old, generally healthy, male who was reported as an **ADO due to dystonia** who also had **"moderate dyspnea," "mild tachycardia," and "mild abnormal vision" in the afternoon of Day 2 of Period 1 after 15 mg Pal given after consuming a high-fat breakfast.** The subject received procyclidine, 5 mg PRN and diazepam (2.5-5mg PRN). These drugs were given i.v. for the dystonia and the dyspnea was treated with oxygen (4L/min) and 1-2 puffs of salbutamol. It is possible that the dyspnea and tachycardia were related to the subject experiencing dystonia (a drug-related event).*

See sections 7.1.8.3.1on vital signs in fed versus fasted conditions and 7.1.12 C for safety results of Phase I studies that examined food effects since the potential for food effects on safety variables were not examined in the Phase II/III trials.

Reviewer Comments on Safety Findings in Phase I Healthy Control Subjects. *It is generally believed that antipsychotic-drug-naïve subjects (who are more likely to participate in Phase I trials of healthy volunteers) have greater risk for some known drug-class effects, such as dystonia. Yet, a recently diagnosed patient with schizophrenia with no prior antipsychotic exposure may also be potentially similar to the healthy subject with respect to risk for adverse drug effects. Furthermore, the schizophrenic population has greater morbidity and is believed by many to have greater risk for mortality than is observed in the general population. Furthermore, patients with concomitant illnesses and elderly are also more vulnerable. Consequently, events occurring in Phase I studies can be useful in understanding drug effects that may be relevant to the schizophrenia patient population, particularly since these trials are generally conducted in more controlled conditions than conditions employed in Phase III studies.*

F. Ischemia-related Events

The sponsor conducted a special search of ischemia-related AEs in which results were primarily provided as the incidence of cases in Phase III safety datasets (as described in Section 7.1.4.5 of this review). The following individual cases that are at least suggestive of ischemia related events were found by the undersigned reviewer upon review of selected narratives or of safety sections of the CSRs for the short-term, placebo controlled Phase III trials.

Subject 502217: This subject was a 49 year old female who developed ***"ischemia" with "possible endocardial injury"*** *revealed* ***by ECG on Day 6 of Pal treatment (9 mg/day)*** *that led to an* ***ADO on Day 9*** *and* ***treatment by a cardiologist, as well as at least 3 weeks of hospitalization.***

In summary, the timing of the onset of these events (within approximately 1 week of treatment) together with vital sign and ECG results described later in this review is suspicious of a role of Pal treatment in exacerbating an undiagnosed cardiac disorder (e.g. coronary artery disease). This review describes vital sign and other cardiovascular related effects that occur near approximately the time when steady state levels are expected to achieve and effects near Tmax. Although, subject 502217 had a history of hypertension and a baseline ECG showing NSST wave changes and incomplete right bundle branch block, she had no previous history of angina and the timing of these events occurred within approximately 1 week of Pal. Her condition continued after cessation Pal treatment, despite receiving multiple cardiac medications that included isosorbide dinitrate 20 mg BID (an "internist-cardiologist" was consulted. Despite this treatment regimen which started on Day 9 the ECG abnormalities persisted (as assessed on Day 17). A failure of the "ST depression, possible endocardial injury in the inferiror leads (II,III and AVF)" that were first observed on Day 6 of Pal treatment, despite treatment with isosorbide dinitrate is highly suspicious of myocardial infarction (MI or

at least endocardial infarction). Although, results of a cardiac work-up to rule out an MI could not be found in the narrative of this subject (e.g. enzyme levels could not be found).

The following are more details on this subject. This subject (in the 9 mg Pal group of Study 305) who ***had abnormal ECGs of "ischemia"*** *during Pal treatment that was reported as an* ***ADO due to "ischemia" on Day 9 of Pal.*** *She was not described as having any abnormal vital sign parameters but had borderline hypertension (140/85) on Day 6 of Pal treatment. An ECG assessment* ***on Day 6*** *of treatment showed* ***ST depression, and "possible endocardial injury inferior leads" and "incomplete right bundle branch block."*** *Ischemia was reported as an AE on Day 8. Study drug was stopped on Day 9 due to "inferior ischemia."*
The above ECG abnormalities were also noted on an ECG assessment on Day 17 (8 days after the day of Pal treatment cessation). The baseline ECG showed non-specific ST wave abnormalities with "incomplete right bundle branch block." Other baseline safety assessments were generally within normal limits or did not reveal any clinically remarkable except that GGT was reported to be elevated at baseline. No other information to explain these events could be found in the narrative for this subject (e.g. a description of cardiac enzyme levels and post treatment cessation ECG results could not be found other than a comment that "a slight improvement occurred in the ECG" at the time of discharge from the hospital 3 weeks after discontinuing study drug).

Subject 200302 in the elderly Phase III trial (study -302) had the ***SAE and ADO of "acute coronary syndrome" on Day 16 (on 9 mg Pal/day).***

In summary, this subject, who is described in more detail below, appeared to have pre-existing cardiovascular disease and potentially undiagnosed coronary artery disease (and undiagnosed angina). One of the pre-dose ECGs of this subject showed NSST wave changes with isolated premature ventricular contractions while other pre-dose assessments were normal, which suggests that this patient had undiagnosed coronary artery disease and possibly undiagnosed angina. This elderly woman had an unremarkable PMH but had baseline/screening BP of 150/60 and 165/90 (so she appeared to have undiagnosed hypertension).

During Pal treatment, this subject developed hypotensive episodes (it is not clear if she had orthostatic hypotension, as well) and exhibited wide fluctuations in vital signs that apparently did not appear to exist at baseline (hypotensive episodes were first noted during treatment rather than prior to treatment in the narrative description found on this subject and as described later). She was also receiving rescue lorazepam treatment (1-3 mg/day) that may have played a role.

The hypotensive episodes (that fluctuated with hypertensive episodes) appeared to be followed by NSST wave changes on Days 4 and 5 prior to initiating an antihypertensive agent that was started on Day 6 of Pal. A role of this antihypertensive agent in exacerbating the hypotensive episodes should also be considered in events that later occurred (she was diagnosed with "acute coronary syndrome" of "unstable angina" on Day 16 that lead to transfer to a cardiology unit). It is important to note that the recommended starting dose of the antihypertensive agent given to this subject (felodipine) is 2.5 mg, daily for elderly patients (according to Micromedix, the subject was in Greece). This subject was started on a daily dose of 5 mg (as described below).

A role of Pal in inducing hypotensive episodes in a patient with an underlying and undiagnosed cardiovascular condition is suspected given the timing of events relative to Pal treatment. Since this patient was likely to have compromised cardiac output (undiagnosed), her vulnerability and sensitivity to cardiovascular effects of Pal were likely to be greater than in a patient without underlying cardiovascular disease. Any Pal induced changes in vital signs were likely to further compromise cardiac output and hypotensive episodes. Ultimately an antihypertensive agent was given that may have interacted with Pal to further exacerbate this subject's already compromised cardiovascular system. The timing of the events (hypotensive episodes and ECG changes began early in treatment prior to initiating an antihypertensive agent. This timing is suspicious of a role of Pal, given that vital sign and ECG effects appear within the first week of treatment and as described later in this review. Finally, a role of Pal is not surprising from a mechanistic standpoint.

See sections below in this review on vital sign and ECG changes observed within the first week of treatment. Also see previously described subjects with vital sign events occurring within one week of treatment.

The following are more details on the above subject (as found in the narrative of this subject):

"Subject 200302 (paliperidone 6-9 mg, preferred term: acute coronary syndrome; [redacted] was a 66-year-old white woman with a diagnosis of paranoid schizophrenia. Her medical history and physical examination at screening were normal. The CIOMS reported a history of hypertension (diagnosed at age 62). There was no history of cardiovascular disorders. Laboratory values at screening (Day –6) showed increased lactate dehydrogenase; no screening values were provided for red blood cell count or hemoglobin. Baseline laboratory values showed increased lactate dehydrogenase and decreased hemoglobin. She discontinued haloperidol 15 mg on Day –11, lorazepam 8 mg on Day –7 and biperidin 4 mg/day and quetiapine 400 mg/day on Day -5. The subject received rescue medication lorazepam 1 to 3 mg/day on Day 1 and Day 8. There were no concomitant medications reported at baseline.
At screening (Day -6), the ECG showing normal sinus rhythm with monomorphic isolated ventricular premature beats and non-specific T-wave abnormality was read as abnormal, not clinically significant. The baseline ECG (Day -1) was read as normal sinus rhythm and normal repolarization pattern. On Day 4, the ECG was read as normal sinus rhythm and non-specific T wave abnormalities, a second ECG on Day 4 and the ECG of Day 5 were read as normal sinus rhythm with non-specific T wave depression. The ECG on Day 8, 9 and Day 15 were read as normal sinus rhythm and non-specific T wave abnormalities, not clinically significant.
At screening (Day -6), the subject's blood pressure was 165/90 mmHg (standing) and 160/90 mmHg (supine); her pulse rate was 76 bpm (standing) and 72 bpm (supine). Her weight was 65 kg (body mass index 27.8 kg/m2). At baseline, standing blood pressure was 150/60 mmHg and pulse rate was 76 bpm, the supine blood pressure was 140/60 mmHg and pulse rate was 80 bpm.

The subject's standing blood pressure during the study ranged from 95/55 mmHg to 175/90 mmHg and standing pulse rate ranged from 78 to 108 bpm. Supine blood pressure during the study ranged from 110/60 mmHg to 175/70 mmHg and supine pulse rate ranged from 79 to 94 bpm. Felodipine 5 mg/day was started on Day 6 for hypertension.
The subject complained of breast pain on Day 16 while receiving paliperidone 9 mg/day. An ECG was abnormal and she was transferred to the cardiology unit of the general hospital on Day 16 for unstable angina. The subject was diagnosed with *acute coronary syndrome* (acute coronary syndrome-verbatim). Paliperidone 9 mg/day was permanently stopped on Day 16. The acute coronary syndrome was considered serious (life threatening) (source: CIOMS).
The subject received treatment on Day 23 with acetylsalicylic acid 100 mg/day, clopidogrel 15 mg/day, diltiazem 60 mg t.i.d., ferric hydroxide polymaltose complex 100 mg/day, folic acid 30 mg/day, isosorbide mononitrate 20 mg b.i.d., omeprazole 20 mg/day, and perindopril 4 mg/day. Lorazepam 8 mg and temazepam 20 mg were given; she then received risperidone 4 mg b.i.d. The subject was released from the cardiology clinic on Day 23 having recovered without sequelae. She had no complaint of chest pain and an ECG was normal (source: CIOMS).
The acute coronary syndrome was considered resolved in 8 days. The investigator considered the acute coronary syndrome as severe and doubtfully related to study medication.
The subject received paliperidone 6-9 mg/day for 16 days and prematurely discontinued from the study on Day 23 as a result of the serious adverse event acute coronary syndrome.
Angina pectoris has not been reported with the use of paliperidone. The subject's cardiovascular history was unremarkable, except for hypertension since the age of 62. The event occurred on Day 16 of treatment with paliperidone 9 mg/day. The subject was permanently discontinued from the study and no rechallenge was performed. Taking these facts into consideration, a causal relationship between the serious adverse event and the intake of paliperidone cannot be excluded. (Manufacturer's Control No.: GR-JNJFOC-20050406978)."

Additional Subjects of Potential Ischemia-Related Events during Pal Treatment in OL Trials:

- *Subject 500603: This subject was previously described under Subsection B (on tachycardia in the absence of concurrent orthostatic hypotension).*
    - *This subject was a generally healthy 18 year old (Malaysian) with an unremarkable PMH and taking no concomitant medications. This subject had an* ***SAE of tachycardia on Day 4 of OL 9 mg daily of Pal in Study -705 that persisted and was possibly associated with abnormal ECG of NST-wave abnormalities, dyspnea upon exertion and lethargy that was eventually reported as an ADO on Day 22 due to these AEs.*** *See details in the previous description in which this subject had previously received 9 mg daily of DB Pal, but was withdrawn from this 6-week lead-in study due to "lack of efficacy." The*

cardiologist considered the ECG to have invalidly placed precordial leads. The narrative does not describe a repeat ECG performed on this day. Given the young age of this subject and unremarkable PMH the events are likely to be drug related. The subject's ethnicity (Malyasian) may also be a contributory factor (refer to Section 7.1.12 of a Phase I study in Asian (Japanese) and Caucasian subjects.

- *Subject 500849: This subject was a 22 year old generally healthy male with an unremarkable PMH and no concomitant medications described in the narrative (and no abnormal ECGs) who had* ***intermittent NSTW abnormalities on ECG*** *on Day 15 and 36 ECG assessments (normal on Day 29)* ***during DB olanzapine treatment (10 mg/day)****. The* ***Day 36 abnormalities persisted when he was switched to OL Pal (9mg/day)*** *that resulted in* ***an ADO on Day 2 of OL Pal.***

  The narrative does not specify this subject's vital signs, if an ECG changes were only found on some of the leads, if any diagnostic evaluations were conducted (e.g. stress test), if events resolved upon dechallenge or other clinically relevant information. However, given the young age of the subject and unremarkable PMH in the absence of concomitant medications, this ECG event is likely to be drug-related and the potential of ischemia or conduction changes need to be considered.
- *Subject 201139: This* ***40 year old woman had an unremarkable PMH and no concomitant medications*** *who* ***developed "exercised induced ischemia" on Day 7 of 9 mg daily OL Pal treatment*** *in Study -703* ***reported as an ADO*** *that was then treated with deplatt A and pantoprazole with outcome of the event reported as "unknown."*

  The subject had no AEs on a lower dose of Pal, given during the DB 6-week lead-in study (at 6 mg/day). It is possible this subject had an underlying, yet undiagnosed condition but in the absence of other information (which could not be found in the narrative) a role of the study drug is considered probable since it occurred shortly after receiving a higher dose of Pal than she previously received and given the known cardiovascular effects of Pal. Even if she had undiagnosed cardiovascular disease a contributory role of Pal is suspicious given that the event occurred within days after receiving the higher dose-level of Pal.
- *Subject 300347: This 44 year old male subject had* ***no past history of cardiovascular disease of bundle branch block (BBB) and concomitant medications were not reported.*** *He had the* ***SAE of "abnormal ECG (BBB)" reported on Day 57 of 9 mg daily of OL Pal*** *in Study -704 (he previously received DB placebo in the lead-in phase). "Study medication was stopped and he did not require hospitalization." He also had* ***"sinus tachycardia," SST changes "possibility secondary to QRS abnormalities, "prolonged QTc (Bazett) interval of 495 msec"*** *and a* ***QTcF of 444 msec****. Standing and supine* ***pulse were 120 and 117 bpm,*** *respectively. QTc Bazett's is not an appropriate method when HR is increased.*

  It appears that this subject developed sinus tachycardia and the possibility of ischemia should be considered (but information is limited on this subject), along with conduction defect. BBB is not atypical in the general population and this subject may have had an undiagnosed, underlying condition. However, given the information as presented in the narrative, at least a role of Pal treatment is suspected. He was later on Day 65 "withdrawn from the study because of incarceration."

- *Subject 501572 (found in the 120-Day SUR): This subject is a 46 year old woman with an unremarkable PMH and normal assessment on screening (no concomitant medications reported) who had **"heart attack" ("myocardial infarction) reported as an SAE while receiving OL Pal (9 mg/day)** that resulted in an **ADO and hospitalization**. She first had "coronary and aortic atherosclerosis, heart failing and ischemic heart disease" reported on Day 32 of the OL Pal treatment. **Her Pal dose had been increased from 6 mg daily.** However, she had received the higher 9 mg daily dose on Days 1-14 of OL treatment due to "mild anxiety" on Day 14. She also received 9 mg daily of Pal in the DB lead-in study. She was discharged from the hospital on Day 62 after receiving multiple heart medications "having recovered without sequelea" and was discharged on clopidogrel and isosorbide mononitrate.*

  While an undiagnosed coronary artery disease may have been a pre-existing condition (not clear how this was ultimately diagnosed since diagnostic testing and results were not found in the narrative), a role of Pal appears to be likely as a potential contributory factor in exacerbating a potential underlying condition after the Pal dose had been increased. Although, she previously had received this dose without an SAE of "heart attack," it is possible that a combination of factors (along with potentially undiagnosed underlying heart disease) including a dose increase of Pal contributed to her SAE.

The following Phase I subjects were found in Phase I/II line-listings and narratives (copied from the narrative descriptions):

Subject 101116 (myocardial infarction), a 79-year old white man in the elderly subject group with no prior clinically significant medical history of cardiovascular problems or physical abnormalities showed signs of an inferior myocardial infarction on the ECG recording 5 days following the final repeated dose of ER OROS paliperidone. The adverse event resolved within 17 days, without treatment intervention or hospitalization. The subject was seen in the hospital and was prescribed Aspirin cardio 80 mg q.d. as prophylaxis. The event was considered possibly related to the study drug by the investigator. Subject was referred and seen by the cardiologist 55 days after the end of the study. Upon completion of a stress test the subject was told to continue his aspirin cardio. The subject will be followed up in a year by the cardiologist.

***Reviewer Comment.** This subject was likely to have undiagnosed cardiovascular disease, yet a role of Pal in leading to this significant cardiac event since it's not clear form the narrative what previous ECG, vital sign and laboratory measures showed or other relevant information (e.g. results of a diagnostic work-up). This patient could have developed episodes of altered vital signs induced by Pal that further compromised his cardiac output or he may have had undiagnosed congestive heart failure that was further compromised with episodes of ischemia such that by the time of his fifth dose he had an unstable condition and ultimately suffered myocardial infarction (cardiac enzyme results could not be found in the narrative).*

The following additional subject in Study -301 was found in the 120-Day SUR (this study was recently completed prior to this SUR):

- *Subject 100067 had the **SAEs of "hypertension urgency," "chest pain" (a "heaviness in her chest" with "tingling in her left arm") and tachycardia on Day 21** of DB treatment of 9 mg daily of Pal (she completed run-in and stabilization phases with the first AE of "elevated blood pressure" on Day 14 of DB treatment. These events **recurred on Day 21 (chest pain tachycardia and hypertension), along with non-specific STT-wave changes (not previously observed) with "short" QT and QRS intervals on an emergency room ECG assessment that lead to Pal treatment cessation.** While this subject had risk factors, including controlled hypertension and diabetes she had not previously reported history of cardiac related events (such as no history of angina). Another non-drug-related factor is that the subject may have "possibly missed doses" of her ongoing antihypertensive agent since Day 18 of the DB phase. Nevertheless a potential contributory role of the drug is considered given that there was no reported history of angina in this subject.*

G. QT prolongation

See sections later in this review describing QT prolongation effects that ~~appear~~ to exist near Tmax, at least early in treatment that appear to resolve over time (but this is unclear since ECG assessments after several weeks of treatment were conducted less frequently and not tightly controlled to capturing peak levels with the daily dosing regimen). However, a small numerical QT prolongation appears to exist after over 6 months of treatment described under section 7.2.9.1 of this review (results in the 120-Day SUR) that appears to be supported by results on the incidence of outliers that were found in the 210-Day SUR (under Section 7.2.9.2 of this review). However, outlier results in a longterm OL study are more difficult to interpret since the longer and more frequently a subject is monitored the more likely outliers will be detected (due to background noise alone). Since the sponsor did not look at outliers for low QT values then it is not possible to determine if outliers were also increased over time with low values which would support a non-drug-related trend on the incidence of outliers over time in these OL trials.

Previous subsection describes subjects that had QT prolongation reported among with other cardiovascular related events, such as the following previously described subjects:

- *Subject 201022 under Subsection B (on tachycardia in the absence of concurrent orthostatic hypotension) in a 12 mg Pal subject who had QTc prolongation reported on Day 4 of QTcB of 486 msec which was normal at baseline (along with increased HR). The subject was an ADO due to SAEs of increased HR and BP on Day 7. See a description below, as found in the CSR of Study -303 which provided more details on QT results at multiple time-points.*
- *Subject 201102 in the 12 mg Pal group who had QTcF of 450 msec on Day 6 that resulted in an ADO see below which has the description found in the CSR of Study -303 and provides more details on QT values at various time-points.*

Upon review of the CSRs for these 3 short-term Phase III trials the following subjects were noted:

- *Only 1 subject (a **12 mg Pal subject** in Study 303) had a QTcLD interval that increased from a normal value at baseline **(QTcLD pre-treatment average value of 408.3 msec) to 456 msec on Day 8** (found on page 153 of the CSR. No other information could be found on the subject including the subject number.*
- *One **12 mg Pal subject** in Study 303 (20112) was only 23 year old male with no remarkable medical conditions, no concomitant medication or other potential conditions to account for the following event). This subject was an **ADO due to "ECG specific abnormal (QTcB ≥ 500 msec on Day 6)** and was described in the CSR (on page 155) as showing an **over 60 msec prolongation of QTcLD on Day 6** compared to the baseline value (pre-treatment average value). This subject is described in more detail on page 156-7 of the CSR as also developing **increased HR and increased BP first noted on Day 5** of treatment **(130 bpm HR and 140/90 mmHg BP at supine, 140 bpm HR and 142/90 mmHg at standing compared to baseline values of 77bpm and 120/84 BP at supine and 90 bpm HR and 122/84 mmHg at standing).** "No ECG was available" when these vital signs were obtained on Day 5. However, on Day 6 an ECG showed QTc prolongation (for any QTc method employed) from **approximately 370 to 375 msec (pre-treatment average) for QTcF, QTlc and QTcLD to approximately 440 to 450 msec for QTc F, QTlc, and QTcLD at 4 hours post-dose on Day 6. QTcB** at this time-point was **505 msec compared to 387 msec at pre-treatment** (given increased HR this value is considered an over-exaggerated estimate of the actual magnitude of QT interval prolongation). **QTc interval values (for all QTc methods) returned to baseline** values **on the ninth day (Day 16 of the study) after stopping Pal treatment and HR was only 67 bpm (near baseline values)**. BP values could not be found in the sponsor's description in the CSR on page 157. This subject was previously described under Section 7.1.2.*
- *Subject 201022 in Study 303 was previously described under Section 7.1.2 who was in the 12 mg Pal group (45 year old male and no other conditions or medications to account for the adverse events). The subject was an **ADO on Day** 7 who was reported to have **SAEs of hypertension and tachycardia**. Increased heart rate and blood pressure were **first noted on Day 4,** as well as the **SAE of "prolonged QTc interval) on Day 4 (QTcB of 486 msec compared to 396 msec on pre-dose Day 1 ECG). Heart rate increased to 124 bpm compared to 71 at baseline** and **supine BP increased to 180/114 mmHg** (standing was 170/110 mmHg) **compared to supine BP of 134/90 mmHg at baseline** (130/90 standing). **At 9-days (Day 16) after discontinuing pal treatment HR and BP returned to baseline values** (supine BP was 130/90 and HR was normal). QTcF, QTc sagie derived or linear derived values were not provided in the description of this subject on page 145 of the CSR. QTcB changes were probably an over representation of potential QT prolongation effects since heart rate increased (such that QTcB values would be expected to be falsely high). Yet, consideration should be given to a small Pal effect on increasing QT interval in this subject.*

- *The CSR of Study 305 only describes one subject (subject 500424) in the section on QT interval results who was in the 3 mg Pal group and was an ADO due to "ECG abnormality [STT]". It appears from a description of this subject found in Seciton 6.4.3.1 of the CSR that this subject had an abnormal ECG at baseline as well.*
- *Subject 500407 in Study -305 had QTcB prolongation reported as an AE and syncope as an AE (other QT values could not be found in the narrative) is described under Section C on Cardiovascular related events associated with syncope.*
- *Subject 300444: an ADO due to QTc prolongation in Study -304 after 7 days of 6 mg Pal treatment with Day 5 QTcB of 502 msec (compared to 464 msec at baseline) and QTcF of 456 msec (baseline value not found) who also had a HR of 106 on day 5. Prolonged QTcB resolved by Day 8 (468 msec).*

The CSRs of the short-term trials had section on QT prolongation that included a description of several subjects with QTc interval increases during Pal treatment but were not reported as ADOs or SAEs. Some of these subjects showed normal values and baseline and showed increases during treatment. Only 2 subjects increased from normal at baseline to prolonged during Pal treatment (prolonged is defined as over 450 msec in males or over 470 msec in females) while 6 subjects showed normal values at baseline and had borderline values during treatment (defined as over 430 msec in males and over 450 msec in females). The increase in QT interval often occurred within approximately one week of treatment and generally following a daily dose increase to 9 mg in several subjects. Although there were 2 subjects showing elevations near Day 40 of treatment.

"Mild" AE of ventricular arrhythmia along with the AE of QT prolongation was reported in one of the subjects (200614) found in the CSRs, as above. These events occurred on Day 15 on the day of a daily dose increase from 6 mg to 9 mg, daily, as described in the CSR. This 65 year old female subject did not have any past medical history or concomitant medication to explain these events. Furthermore, the predose QTc average values were normal and then increased to the following values on Day 15: 451 to 454 msec for QTcLD, QtcF and QTlc intervals and 471 msec for QTcB interval. Despite these events, the subject completed the study without subsequent QT interval or vital sign related events and had normal vital signs throughout the study.

<u>Subjects in the elderly Phase III trial:</u>
2 ADOs occurred in the elderly Phase III trial (-302) that included events of QTcB prolongation (subjects 200514 and 200119) of over 450 msec. One of the subjects had QTcF values of over 500 msec. The QT prolongation was reported on Day 4 of 6 mg daily in these subjects (one had increased heart rate).

<u>Subjects in OL Trials:</u>

- *Subject 201418 was found in a 120-Day SUR in which the role of Pal in QT prolongation (QTcLD of 549 after approximately 6 months of OL 9 mg/day Pal treatment) is unclear, as described in section 7.2.9.2 of this review.*
- *Subject 200214 was previously described who died form what appeared to be due to multiple factors in which Pal may have played a role and in which QT prolongation*

was also reported among other events prior to death (see section 7.1.1 on deaths for details).

- ***Other cases may have existed but due to the late date of the 210-Day SUR submission in the review cycle very little of this submission was reviewed.***

Additional subjects in a recently completed Study -301 found in the SUR:

- ***QTc prolongation of up to 461 msec (QTcL and QTcLd)*** *lead to an* ***ADO*** *in Subject 100232 on Day 57 of 9 mg Pal daily during the run-in phase of Study -301. QT prolongation resolved upon treatment cessation. QTc prolongation was reported to resolve in 22 days in the narrative description (page 1790 of the SUR) but it is not clear if any previous ECG assessments were conducted following treatment cessation. Furthermore, risperidone was initiated after 3 days of stopping Pal treatment (no ECG value is found in the narrative). The narrative provides limited information on ECG values over time. In the absence of more information, a role of the study drug cannto be ruled out. This subject (a 56 year old generally healthy white male) had a history of bradycardia (52-56 bpm during screening). Bradycardia can influence QT interval values but may also pose a potential risk for development of QT prolongation. Even when QT was corrected for low heart rate the value was still clinically prolongated (QTcB of 458 msec on Day 57 while HR was 57 bpm). The subject was not included in the "interim analyses." Refer to the last section of this review for further comment and recommendations regarding QT interval effects.*
- *Subject 100767 was a 31 year old, generally healthy male with unremarkable PMH, on no concomitant medications, normal baseline ECG who also had* ***QTc prolongation on Day 8 at 10 hours post-dose after 12 mg Pal, increased from 9 mg daily on previous study days that lead to an ADO on Day 16.*** *QTcB, QTcL and QTcLD showed a "borderline" prolongation of up to 467 msec for QTcB (heart rate values could not be found in the narrative). QTc prolongation was intermittent which is not surprising since QT effects were found to be time-dependent in the short-term trials. While the investigator considered the QTc prolongation to be moderate in severity and "probably" drug-related the prolongation "did not resolve." QTc values after Pal treatment cessation could not be found in the narrative.*
- *Subject 100336 was an* ***ADO due to prolonged QRS complex on Day 10*** *(but not on the Day 4 ECG assessment) while receiving* ***12 mg Pal treatment*** *(in the run-in phase)* ***that resolved upon dechallenge*** *(based on a Day 17 ECG assessment). This initial study phase used a flexible dose design (a description of what the starting dose in this trial cannot be found in the submission but could have been 9 mg daily which was the starting dose in the OL extension trials -702-705). It is not clear in the narrative when the dose of Pal was increased in this subject. This 50 year old woman was generally healthy with an unremarkable PMH. Concomitant medications were sertraline from Day -4 through Day 10 and rescue lorazepam treatment during the study. This subject had an abnormal ECG at baseline that did not involve "QRS" prolongation or "heart block" (baseline ECG showed nonspecific T-wave abnormalities, low voltage QRS and an RSR' pattern in V1).*
- *Subject 100320 was an* ***ADO due to T-wave inversion on ECG on Day 4 (at 4 hours, 10 hours and 22 hours post-dose assessment time-points) of 9 mg daily of Pal (in the***

run-in phase). *The subject also had* ***low blood pressure in the absence of tachycardia (118/81 mmHg and 84 bpm at standing compared to baseline standing values of 136/80 mmHg and 82 bpm).*** *This 53 year old WM had a history of an old MI with ECG findings with this history, along with nonspecific ST wave changes at baseline. However, at post-dose time-points early in treatment that appear to be characteristic for drug-induced hemodynamic effects (refer to previous sections of this review for time-dependent changes on ECG parameters), this subject developed T wave inversion and a new RSR' pattern on the V1 lead "suggestive of myocardial ischemia." Therefore Pal was discontinued on Day 6 and ECG changes resolved in 10 days. "Mild tachycardia" was reported as an AE 7 days after the last Pal dose (100 bpm standing and 106 bpm supine). Although a pre-existing condition could explain ECG changes, the ECG changes occurred at early in treatment at time-points that are characteristic of time-dependent drug effects (on ECG parameters) observed in the short-term phase III trials at this daily dose-level as previously described in this review. Furthermore, the event resolved upon dechallenge and given the long half life of Pal, it is not surprising that resolution did not occur until 10 days post-dose. The development of a decreased systolic blood pressure in the absence of tachycardia at the post-dose time-points early in treatment is also highly suspicious of drug-induced hemodynamic effects. The absence of tachycardia is also noteworthy since tachycardia would be expected at these time-points. Tachycardia was reported as an AE after 7 days of Pal treatment cessation and was reported to persist (while ECG changes resolved, 10 days post Pal cessation). It is important to note that the subject was taking mirtazapine as a concomitant medication at baseline, which could potentially influence findings but would not explain the timing of ECG and vital sign changes during Pal treatment.*

H. Potential Cerebrovascular-Related and/or Additional Potential Cardiovascular Related SAEs and Other Clinically Remarkable Events

Grand mal Convulsion (SAE) was reported in a 23 year old patient who was found to have a positive MRI for an "old lacuner infarct in the left thalamic nucleus" in S300676. *The description of this subject (below) is consistent with a seizure (tonic clonic) and the EEG was positive (as described below). No pre-existing condition or concomitant medication or other etiological factors can be found in the description of this subject other than the positive MRI finding. However, it is not clear how a 23 year old would have an "old lacunar infarct" and it is not clear to the undersigned that the seizure was not the result of at least a drug-related excacerbation of an underlying condition (e.g. possible cardiovascular or cerebrovascular system effects or a possible effect on seizure threshold or some other effect).*

See a more detailed description below found on pages 131-132 of the CSR for Study -304:

Subject 300676, 23-year-old white man, ER OROS paliperidone 6 mg group: This subject had no past history nor family history of seizure or epilepsy. On Day 5, the subject experienced a "grand mal convulsion". The tonic-clonic seizure lasted about 45 seconds; he hit his head, sustaining a 2 cm laceration to his left forehead when he fell, bit his tongue and shook violently. He was not incontinent, but was incoherent, lethargic, and

somewhat unresponsive after the seizure. Intravenous treatment with fosphenytoin sodium was initiated. The subject was scheduled to have an electroencephalogram (EEG); prior to the EEG, he apparently experienced another tonic-clonic seizure. There was no convulsive activity noted during the EEG. This report showed a diffuse slowing and triphasic waveform that suggested an underlying metabolic encephalopathy with a structural lesion and probably represented continuous seizure activity. On Day 6, a magnetic resonance imaging revealed evidence of an old lacunar infarct in the left thalamic nucleus, otherwise the examination was normal. Treatment with aripiprazole, atenolol, and phenytoin was initiated on Day 6. The grand mal convulsion, which the investigator considered serious, resulted in the discontinuation of study medication and premature discontinuation from the study. The investigator assessed the grand mal convulsion as severe and possibly related to study medication. The adverse event was considered to have resolved in 1 day with treatment. It should be noted that the subject was receiving concomitant pantoprazole; convulsions have been reported in <1% of subjects receiving this medication.

Additional subjects found in the 120-Day SUR or in OL Trials:

- *Subjects 201452 and 300166 were 54 and 53 year old, female and male subjects, respectively that had an unremarkable PMH except for mild hypertension (no antihypertensive agent found in the narrative) in the former subject and hypercholesterolemia in the latter subject. Both subjects previously received DB placebo in the lead-in study but developed "ischemic stroke" (an SAE) and "aphasia" on Day 10 of 9 mg Pal daily in subject 201452 and "transient ischemic attack" (as an SAE) on Day 40 of 9 mg daily of Pal. Vital sign, ECG data and other related clinical information cannot be found in the narratives of these subjects (e.g. diagnostic tests to rule in or out atherosclerotic disease such as evidence for carotid stenosis). Therefore at least a potential role of study drug is suspicious in the absence of information related to potential etiology aside form the possibility of an undiagnosed underlying condition (e.g. atherosclerotic disease related to either hypertension or hypercholesterolemia given their PMH of these known risk factors for atheroslerotic disease).*

  Subject 201452 was hospitalized and the following medications were initiated fenofibrate, magnesium sulfate, and piracetam. It appears that he continued OL pal treatment through Day 299 of the study. The "ischemic stroke" was reported as resolved within 9 days and the aphasia resolved in 48 days since their initial onset and after initiating pharmacotherapy.

  Subject 300166 received Pal treatment intermittently (on Days 12 for unclear reasons and Days 41-42 that coincided with the SAE) and ultimately the subject withdrew from the study "due to noncompliance with study medication." Perhaps the Day 12 dose was missed due to noncompliance (but this is not clearly stated in the narrative). CT and MRI were reported as showing "no acute disease" or as "negative," respectively (day of neuroimaging was not found in the narrative). The events in this subject resolved withing 3 days of their onset.

- *Subject 200179: This 65 year old female had "confusional" state leading to an ADO on Day 27 of OL pal (6 mg/day). This subject had a history of "cardio sclerosis and cerbro sclerosis," and had completed 43 days of DB pal at the same dose. A description of vital sign, ECG results or other related clinical information could not be found in the narrative. Therefore, at least a contributory role of Pal needs some consideration.*
- *Subject 300129: Developed dizziness and fell on Day 170 of OL 6 mg/day Pal in Study -704 reported as an SAE.*

I. Seizures or Syncope

Another subject (S300693) in Study -304 had a "possible" seizure who had a history of alcohol abuse and recent abuse of alcohol and recent cessation of lorazepam administration for extrapyramidal disorders. It is not clear if this subject actually had a seizure and if this subject did it was likely related to alcohol withdrawal (along with recent cessation of lorazepam).

See additional subjects of syncope described under subsection C on cardiovascular related SAEs Associated with Syncope and under a subsection on potential cerebrovascular-related events (subsection H).

Additional subject found in the 120-Day Safety Update Report and/or in OL Trials:

- *Subject 200986: This was a 30 year old female with an unremarkable PMH and no concomitant medications reported in the narrative who had an SAE of "generalized tonic-clonic convulsion" reported on Day 13 of OL 9 mg daily of Pal in Study -703 that resulted in an ADO. She had a "sudden onset of tremulousness of hands and feet followed by a fall...frothing at the mouth, and loss of consciousness lasting...about 5 minutes" without "incontinence, injury, tongue biting or postictal confusion reported." An EEG 2 days later was WNL and the subject was lost to follow-up. The narrative does not described any vital sign or ECG results, laboratory results or other clinically relevant information that would lead to potential etiologies. Furthermore, it is not clear if this subject experienced a seizure or some other type of syncopal episode. The absence of a post-ictal state is highly suggestive of a non-seizure related syncopal episode. Although this subject had already received DB Pal (12 mg/day) in the 6-week lead-in study, at least a role of Pal is suspect in the absence of clinical information that would suggest potential non-drug-related etiologies.*
- *Subject 500108 (SAE and ADO): had convulsion reported, hyponatermia, psychogenic polydipsia, aspiration pneumonitis and exacerbation of schizophrenia reported. This subject had undifferentiated schizophrenia who had a history of psychogenic polydipsia. Psychogenic polydipsia has been reported in this patient population which can lead to these other events of hyponatremia, convulsion and aspiration pneumonitis.*

J. Suicidality and Other Mood-related Event (e.g. agitation, aggression, depression).

This topic is covered under Section 7.1.4.6 of this review, based on the sponsor search for suicidality and other related events. A slightly larger incidence of suicidality was found for suicidality in the 15 mg Pall group compared to other treatment groups and placebo, as described in Section 7.1.4.6. Agitation, mood changes, and aggression are expected events of the patient population and in the presence of lack of efficacy of placebo and/or study drug. Section 7.1.4.7 discusses the sponsor's results on their special search for aggression or agitation related AEs that failed to reveal a greater incidence in these events in Pal subjects compared to placebo subjects.

The following descriptions is regarding subjects with suicidality who did not appear to have a clear risk factor for suicidality (aside from schizophrenia) that were found by the undersigned reviewer and are not discussed in Section 7.1.4.6:

A few Pal subjects had suicidality who did not have a clear risk factor for suicidality (e.g. was not reported to abuse substances and did not experience a recent major stressor) other than the known risk associated with this patient population. Many of these subjects were exhibiting signs of experiencing a poor response to Pal treatment or lack of efficacy that would suggest that suicidality was related to their underlying condition together with failure the Pal treatment in adequately relieving these patients of their symptoms of schizophrenia, as described in the following:

- *In Study -304 the CSR described the following subjects who had no reported co-existing or pre-existing conditions that are known to increase risk for suicidality (other than the presence of schizophrenia, of which suicidality more frequently occurs than in the general population):*
  - *Subject 300011in the 12 mg Pal group had SIs along with "increase of symptoms of schizophrenia" with hallucinations and as reported as "wanting to kill herself." This subject was hospitalized and withdrawn on Day 19 from the study due to lack of efficacy.*
- *In Study -305 the CSR described the following subjects who had no reported co-existing or pre-existing conditions that are known to increase risk for suicidality (other than schizophrenia):*
  - *3 mg Pal subjects (500625, 50128): One subject (50128) completed the study which the SI occurred on Day 44 and resolved within 1 day before completing the study on Day 45. This subject's CGI was score was rated as severe at baseline and marked on Day 45, suggesting poor to no Pal treatment response to this low dose-level. The SI in the other subject (50625) was transient (reported on Day 28 and resolved in 4 days). He chose to withdraw from the study several days later after he also reported AEs of palpitation, tremor, lethargy and ambivalence on whether or not to continue in the study. This subject also showed evidence of little to no response to this low dose level of Pal treatment (rated on CGI as moderate at baseline and on Day 36, the day of early withdrawal from the study).*
  - *Two 15 mg Pal subjects in Study -305 who had no reported co-existing or pre-existing conditions that are known to increase risk for suicidality had SIs. One subject (500514) who also had intermittent anxiety (as an AE), completed the study. This*

subject's who had a CGI score that did not change from baseline to Day 43 (assessed as "moderate" on these study days). The other 15 mg Pal subject also had SIs (500623) who also had hallucinations, was "unable to stay calm" and had insomnia with "vague" SIs. He took 9 study drug tablets "and then another 3 tablets"(a 60 mg dose "to calm himself" according to that described on page 141 of the CSR). The patient was hospitalized and received sulpiride and zuclophenotixol acetate. He then improved. He chose to withdraw from the study after about a week following resolution of his AEs, although his CGI score was assessed as marked on the day of withdrawal (Day 23 and also marked at baseline). CGI score was assessed as moderate on Days 4, 8 and 15. The etiology of these SIs are likely to be associated with a lack of efficacy and the known risk of sucidality in this patient population.

- *Only 1 Pal subject is described in the CSR of Study -303:*
  - *This subject (201559) had "cut is arm superficially" and only required topical treatment on Day 23 of 9 mg Pal treatment. This subject withdrew from the study on Day 30 due to lack of efficacy and had CGI ratings of severe at baseline, marked on Day 15 and severe on Day 22 and throughout there remainder of the study, prior to early withdrawal.*

Several placebo subjects also had SIs that could not be accounted for by a pre-existing condition or risk factor other than the presence of schizophrenia (as previously discussed).

3 completed suicides were reported in Study -305 in the 120-Day SUR:

- *2 placebo subjects (500447 and 50130) and*
- *1 subject who withdrew from the study during screening procedures, prior to the DB phase (and was not assigned a subject number).*

K. Elevated CPK

The following enumerates SAEs and ADOs in Pal subjects, according to the summary tables (shown later in this section of the review for completed Phase III trials and as shown later in Section 7.2.9 in the 120-Day Update report, as provided by the sponsor):

- *1 SAE and no ADOs in Short Term Phase III trials: elevated CPK in a 6 mg Pal subject who had a diagnosis of amebic dysentery (S 200969) in Study 303.*
- *None in the Elderly Phase III Study -302*
- *1 SAE and 1 ADO in the 120Day SUR summary table (on the basis of the line listing found in the 120--Day report the ADO and SAE appear to have occurred in a single subject, number 500501 who also had elevated LFTs as described in subsection M on this topic (was in the OL Extension Trials and occurred after over 6 months of exposure of DB Pal/OL Pal treatment).*
- *Study -301 and OL Extension Study -701: reported one subject with NMS and elevated CPK (10057 described in the next subsection).*

The event of elevated CPK alone is not surprising given the study population and the known safety profile for the drug class. The explanation that the sponsor provides (that can be found in

the SCS) for this safety signal on elevated CPK levels is that this type of an event can commonly occur in this patient population.

However, this review describes clinically remarkable elevations in CPK that was observed in multiple trials including Phase I trials (see the section on laboratory parameter results in this review for a description of Phase I results on CPK) that needs to be addressed.

Phase I trials had a number of subjects with dystonic-like related ADOs or SAEs ("muscle spasms," muscular chest pain, dystonic reactions that were sometimes associated with laryngeal or respiratory system involvement). The narratives generally did not include CPK values.

One narrative was found of a subject in a Phase II schizophrenia trials had a dystonic reaction associated with CPK of 607 U/L (in Subject 100040 in Study -SCH-1010).

Only 1 and possibly another subject appeared to have NMS could be found in the SCS and among SAEs and ADOs in the 120-Day SUR. Subjects with rhabdomyolisis, fever associated with elevated CPK, or extrapyramidal side effects associated with CPK were also not found in the SCS (or in SAEs, ADOs in the 120-Day SUR).

L. Neuroleptic Malignant Syndrome

One case of markedly elevated CPK levels in which NMS was reported (in Paliperidone subject) was subject 100057 who was in a "prevention of recurrence" study (found in the 120-Day SUR). This subject first developed "muscle stiffness in the entire body" on Day 15 of Pal treatment while receiving 12 mg daily (the next to the highest dose-level employed in Phase I-III trials). By Day 22 this subject had marked CPK elevation (temperature was 36.4°C).

At least one other subject may have had NMS who was found in a review of the CSR of completed, short-term Phase III trials. Subject 200213 (in Study -303) was in the 12 mg Pal group (the next highest dose-level employed in primarily non-elderly Phase III trials) and was 66 years old (a potential risk factor) who developed fever (reported as an AE) and "dystonia focalis," "hypersalivations," "blurred speech" on day 3 of treatment ("after 2 doses" upon which treatment appeared to be discontinued at this time). Post-dose laboratory values were not available and the only post-dose temperature was on Day 4 (36.8 degrees C) as described on page 117 of the CSR. The subject was reported to be withdrawn from the study on Day 4 "due to dystonia." The patient received neostigmine injections for 1 day and oral pyridostigmine treatment for 2 days. The "investigator confirmed that the patient did not have NMS." A description of a differential diagnosis and the diagnostic work-up to rule out NMS cannot be found in the narrative. Therefore, it is the opinion of the undersigned clinical reviewer that the conclusion that this patient had NMS cannot be made in the absence of actual clinical data. The clinical description of this subject (fever, dystonia) is suspicious of an NMS-like presentation.

M. Elevated CPK with Concurrent Elevations in LFTs

This subsection describes subjects with elevated CPK that also had elevations in LFTs. A discussion of additional and potentially remarkable subjects with elevated LFTs follows this subsection.

It is notable that some schizophrenia subjects in Phase III trials and some Phase I healthy volunteer subjects showed elevations of LFTs that were also associated with elevations in CPK.

Elevations in LFTs (enzymes) can nonspecific and not always involving the liver. However, at least one of the subjects described below also had elevations in GGT (Subject 501245 in an OL Phase III trial, a copy of the narrative is below) who developed markedly elevated CPK and other LFT values who was an ADO due to choleliathisis (she showed evidence for cholangiitis) that may or may not be drug-related (she had multiple risk factors suggesting an undiagnosed underlying condition and she had already received months of treatment prior to developing this condition). This subject is described in more detail in the next subsection on elevated LFTs.

Subject 500501 is also mentioned in the next subsection (a copy of the narrative is provided below in this subsection) who had elevated LFTs and CPK (up to 688 U/L) similar to the above patient. However, the LFT and CPK elevations were not as marked and fever or elevated WBC or eosinihpilia were not described in the narrative (although mention of laboratory results on these parameters could not be found). The elevated laboratory parameters were first noted on Day 169 of Pal treatment and lead to an ADO on Day 174. No past history or risk factors were described in this 33 year old Asian male patient in one of the OL Phase III trials.

Subject 501320 (also listed in the next section on elevated LFTs) during DB olanzapine treatment in one of the Phase III trials that "persisted" during this study, but were also reported during OL extension trial (-705) of Pal treatment (9 mg/day). These laboratory changes lead to an ADO after 3 days of OL Pal treatment. Although the subject had some elevations in LFTs, values increased during the DB olanzapine and OL Pal treatment phase, along with elevations in CPK that were not observed at baseline (CPK elevations of up to 454 U/l during Pal treatment and CPK of 279 was reported during olanzapine treatment). While these events appeared to be related to olanzapine further increases appeared to be related to Pal treatment.

Copies of the narratives of the above subjects are provided below.

Copies of Narratives of the above subjects:

Subject 500501 (paliperidone dosage at onset of event: 9 mg/day; alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine phosphokinase increased gamma-glutamyltransferase increased; [redacted] was a 33-year-old Asian man with a diagnosis of undifferentiated schizophrenia. His medical history and physical examination results at screening were within normal limits; no history of liver disease or hepatic symptoms was noted. The subject was assigned to receive paliperidone 15 mg/day during the double-blind study, which he completed on Day 35. He received paliperidone 9 mg/day during the

open-label extension study On Day 169, the subject experienced a mild "elevated ALT" 60 U/L (reference range: 6-43 U/L), a mild "elevated AST", 37 U/L (reference range: 11-36 U/L), a mild "elevated CK level", 484 U/L (reference range: 18-198 U/L), and a mild "elevated GGT", 211 U/L (reference range: 10-61 U/L), all of which were persistent. The investigator believed that it was possible for the elevated CK level to be related to the study medication but found it doubtful that the elevated ALT, AST, and GGT were related. The subject had a creatine kinase retest performed at a local laboratory on Day 174 and the results were 688 U/L. No history of liver disease was specified. The study medication was permanently stopped after Day 173 and the subject was withdrawn from the study on Day 174 due to the adverse event. He was referred to an internist for further evaluation (source: CIOMS). (Manufacturer's Control Number: KR-JNJFOC-20050502675(2)).

"Subject 501320 (paliperidone dosage at onset of event: 9 mg/day; hepatic enzyme increased; [redacted]) was a 28-year-old black man with a diagnosis of paranoid schizophrenia. His medical history included a full-remission of poly substance abuse and a nonspecific T-wave abnormality; there was no history of liver disease reported. His physical examination results at screening were within normal limits. The subject was randomly assigned to receive olanzapine 10 mg/day during the double-blind study. Adverse events reported included non-serious events of "moderate elevated liver enzymes" and moderate "elevated CK" increased on Day 44; both events persisted and were considered by the investigator to be probably related to study medication. He completed the study on Day 44 and entered the open-label extension study. The subject received paliperidone 9 mg/day during the open-label study. On Day 1, the non-serious events of moderate "elevated liver enzymes" and moderate "elevated CK" were reported. Laboratory data at double-blind screening revealed elevations in alanine aminotransferase (ALT) 49 U/L (reference range: 6-43 U/L), creatine kinase 279 U/L (reference range: 18-198 U/L) and gamma glutamyl transferase (GGT) 118 U/L (reference range: 10-61 U/L). At double-blind baseline elevations were noted in ALT of 60 U/L, aspartate aminotransferase (AST) 41 U/L (reference range 11-36 U/L) and GGT 114 U/L. On Day 1 laboratory data included ALT 73 U/L, AST 52 U/L, GGT 249 U/L and CK 454 U/L. The subject was not treated and the events resolved within 9 days. The investigator believed that the events were probably related to the study medication. Study medication was stopped on Day 3; on Day 4, the subject was withdrawn from the study due to the event of increased hepatic enzymes."

"Subject 501245 (paliperidone dosage at onset of event: 9 mg/day; cholelithiasis; [redacted]) was a 58-year-old black woman with a diagnosis of paranoid schizophrenia. Her medical history included elevated

triglycerides and diabetes; physical examination was noncontributory to the adverse events. The subject was randomly assigned to receive paliperidone 9 mg/day during the double-blind study. "Nausea", "yeast infection," "abnormal ECG," "headache," "fatigue," and "middle insomnia" were reported as adverse events during double-blind; concomitant medications included clotrimazole, acetylsalicylic acid, amantadine, metformin and multivitamins. The subject completed double-blind and entered the open-label extension study on Day 43. The subject received paliperidone 9 mg/day during the open-label extension study including 9 days without study medication. On Day 192, the alanine aminotransferase (ALT) was slightly elevated at 56 U/L (reference range: 6-34 U/L). The ALT remained elevated on Day 204 at 51 U/L, and 57 U/L on Day 311. The ALT on Day 367 was within normal limits. On Day 295, the serious adverse event "cholelithiasis" was reported. Study medication was temporarily stopped on Day 295 as the subject reported nausea and then confusion, when she stopped taking her study medication (source: CIOMS). She was admitted to the hospital on Day 298 (source: CIOMS) for confusion and right upper quadrant abdominal pain (for the last week), which she attributed to eating spicy foods. Her temperature in the emergency room was 101.7° (later reported to be 99.1°). Diagnostic studies revealed a negative chest x-ray and ECG showed normal sinus rhythm (source: CIOMS). Laboratory results showed sodium 136, potassium 3.4, chloride 96, CO2 30, BUN 14, creatinine 1.2, total protein 7.3, albumin 3.4, glucose 184, phosphorus 1.9, urate 8.2, bilirubin 6.4, alkaline phosphatase 219, CK 938, LDH 543, AST 346, ALT 821, triglycerides 530, total cholesterol 177, TSH 3.91, free T-4 1.1, urine pregnancy test negative, WBC 5.2, hematocrit 32%, MCV 94, platelets 300,000, segs 74%, (no units or ranges provided). A consultation was obtained because of the elevated liver function tests; the subject had no history of liver disease or any family history, no known hepatitis, no history of intravenous drug use, blood transfusion, GERD, ulcers or pancreatitis. The subject denied any abdominal pain but reported that she had nausea without emesis for 1 week after eating greasy food. The subject reported never being a heavy drinker and last drank alcohol 2 years ago (source: CIOMS). Metformin was stopped during the hospitalization. Laboratory analyses showed amylase and lipase to be within normal limits, total bilirubin 3.3, direct bilirubin 1.8, alkaline phosphatase 191, CPT 282, AST 150, and ALT 550 (no units or ranges provided). The physician assessed that the subject's liver function tests exhibited both a cholestatic and hepatocellular pattern. Moreover, given the subject's history of symptoms starting after a greasy meal and dark urine with bile, this likely representedcholestatic disease, possibly caused by gallstones. An abdominal ultrasound was ordered to better evaluate the subject (unknown results). The subject recovered without sequelae and was discharged from the hospital on Day 304 (source: CIOMS). Paliperidone 9 mg/day was resumed on Day 304. The investigator considered the cholelithiasis severe and doubtfully related to study medication. The serious adverse event of cholelithiasis resolved in 9 days. The subject completed the study on Day 367. The other adverse events reported

during the study were "sore throat," "increased triglycerides," "hypokalemia," "rash on chin," "pinched nerve" and "diarrhea" (3 times)."

N. Elevated LFTs

The following enumerates SAEs and ADOs of an elevated LFT were reported in Pal subjects (according to summary tables later in this section for the completed DB Phase III Short-Term trials and in summary tables provided in the 120-Day SUR shown in Section 7.2.9 for OL Studies and Studies -301 and -701):

- *DB Phase III Short-Term Trials (-302, -303, -304, -305) in which subject numbers were found in a line listing in the SCS:*
  - *1 SAE of increased LDH in a subject in the 6 mg Pal group in Study -303 (the line listings show a subject 200969 who also had increased CPK as an SAE who was diagnosed with amebic dysentery).*
  - *4 ADOs of which 3 subjects had abnormal baseline values:*
    - *1 ADO of increased transaminases in a subject (201445) in the 12 mg Pal group in Study -303 who had abnormal values at baseline.*
    - *2 ADOs of increased hepatic enzyme: in a 3 mg subject (that appeared to be drug-related as described below in subject 500853 that was found in the line listings) and a 6 mg Pal subject (subject 201684 who had abnormal baseline values but was receiving risperidone prior to be receiving Pal)*
    - *1 ADO of increased ALT in a 9 mg Pal subject in Study -303 who had abnormal values at baseline.*
- *OL Extension Trials (-702,-703, -704, -705) in which subject numbers were found in line listings in the 120-Day SUR*
  - *Only 1 SAE of a liver function related event (cholelithiasis) can be found in the summary table enumerating SAEs. The LL shows that subject 501245 with cholelithiasis (with fever and leukocytosis) reported as an SAE and leading to an ADO that appeared to be possibly related to an underlying, undiagnosed condition, but this is not certain (in the absence of critical diagnostic data such as ultrasound results; see the previously provided narrative in the above subseciton).*
  - *ADOs of*
    - *1 subject with increased AST, ALT, GGT (GGT was elevated to greater extent than AST and ALT with values of upt to 211 U/l reported in the narrative) and CPK reported as AEs leading to the ADO in a DBPal/OLPal subject in the over 6 month treated subgroup in Study -705 (Subject 500501, according to the line listing in the 120-Day SUR). According to the line-listing on SAEs this subject also had elevated CPK of up to 688 U/l reported as an SAE (as already described above in more detail). These events were first observed on day 169 of OL Pal treatment (9 mg/day). This subject was a 33 year old with unremarkable PMH and no concomitant medications reported in the narrative and the outcome of these events after early treatment cessation cannot be found in the narrative. Therefore, in the absence of a non-drug-related explanation for*

these elevations a role or cause of the study drug is suspected. See the narrative information provided in subsection M above.

- *1 subject with increased hepatic enzyme in the ≤ 6 month DB Olanz/ OL Pal group (according the LL subject 501320 was an ADO due to "elevated liver enzymes"). This subject had elevated LFTs (GGT, AST and ALT) as well as elevated CPK after completing DB olanzapine treatment (in the 6-week lead-in study) but they increased further (up to 5 x ULN for GGT and CPK reach 454 U/L while other LFTs also increased to a lesser extent) on Day 1. Pal was discontinued on Day 3 and these events resolved by 9 days post Pal cessation. These events appeared to be olanzapine related but may have been further increased by Pal. The narrative of this subject was provided under the previous subsection.*
- *An additional ADO was found in the LL (not in the summary table) of cholelithiasis in subject 501245 that was also reported as an SAE.*

- *Study -301 had 1 subject (subject 100737) with an SAE of cholelithiasis that lead to an ADO after only 1 day of treatment in the run-in phase.*

  Cholelithiasis was reported in a 47 year old female (100737 subject) after only 1 day of treatment in the run-in phase that lead to an ADO. This type of event is not uncommon in a 47 year old female and is not likely to be drug-related given that the event occurred only after one day of a 9 mg Pal dose. Cholelithiasis was reported in a 47 year old female (100737 subject) after only 1 day of treatment in the run-in phase that lead to an ADO. This type of event is not uncommon in a 47 year old female and is not likely to be drug-related given that the event occurred only after one day of a 9 mg Pal dose. However, the narrative does not provide any laboratory values (e.g. eosinophil count to determine if eosinophilia was present which would suggest a drug-related cholangitis secondary to an allergic response to the study drug). The 120-Day SUR narrative indicates that an ultrasound revealed cholilthiasis. Therefore, it is unlikely that this event was drug-related.

The sponsor provided narratives for subjects with greater than 3 times the upper limit of normal on ALT or AST but these narratives were generally not reviewed since there were SAEs, ADOs and clinical parameter sections on LFTs that were considered more informative (since many subjects with greater than 3 times of the upper limit of normal had abnormal values at baseline and since the incidence of outliers on LFTs was provided in other sections with results described in this review).

At least some of the below cases are considered likely to be drug-related as described below. Yet, descriptions of individual subjects could generally not be found in any in-text section of the SCS. Given that cases of concern were revealed by the undersign reviewer that were not found in the in-text sections of the SCS the sponsor was inquired about outliers on LFTs, as discussed below.

Refer to the last section of this review for further comments and recommendations.

Inquiry on Remarkable LFT Outliers with a Response Received in a Recent N005 submission with Review of Results Pending:
Since some remarkable cases were found in at least one subject involving up to approximately 8 times the upper limit of normal (ULN) of AST and elevations in other LFTs during 15 mg Pal treatment. This subject could not be found in line listings of SAEs or ADOs or in in-text sections on LFTs in the SCS (this subject, 5013018, is described below). Due to concerns of missing other remarkable cases the sponsor was asked to provide more information about outliers on LFTs (e.g. using specific cut-off criteria for subjects with normal values at baseline and other specifications).

The results of a N005 response to our inquiry was submitted and are summarized in section 7.1.7.3.3 in this review.

Since most narratives describing elevations in GGT (and/or CPK) did not mention laboratory results on WBC and differential it may be informative to ask the sponsor about any cases of elevated LFTs with eosinophilia. Cholangitis (with increased GGT and also generally increased alkaline phosphatase) in the presence of eosinophilia would be highly suspicious of a drug-related event.

In addition to the previous described subjects with elevations in LFT (and/or CPK) the following subjects are noted.

The following are subjects found with elevations in LFTs (±CPK elevations):

- *The following subject was found in the narratives (which were provided for subjects with greater than 3 times the ULN of LFTs) but the subject was not listed as an ADO or an SAE. Subject 503018 in the* ***15 mg Pal group*** *in Study -305 was a 44 year old male with no history or abnormal baseline values suggestive a pre-existing liver disorder who developed approximately* ***8 times the ULN of ALT and approximately 5 times the ULN of AST*** *with about* ***almost 4 times the ULN of GGT on Day 15 of Pal that resolved to normal values after 9 days (on Day 29) following Pal cessation on Day 20.*** *The subject received 12 mg daily of Pal for 7 days (during a titration period) followed by 12 days at the 15 mg daily dose-level.*

The marked elevation in LFTs in the above subject is likely to be drug-related *given the patient's unremarkable past history and normal baseline LFTs, the marked increase in LFTs after a few weeks of a high dose of Pal that resolved upon dechallenge. The elevated LFTs were not reported as AEs and the subject withdrew from the study 4 days after Pal was stopped (on Day 20, LFTs were elevated from Day 15, "onward" and normalized on Day 29). The narrative doesn't say why Pal was stopped on Day 20 and the subjects was not listed as an ADO. The narrative says he withdrew from the study on Day 24 "due to non-compliance." This subject was found in the narratives, but a description of this subject could not be found in in-text sections in the SCS or in in-text sections of the Study Report for Study 305 (e.g. sections in the SCS and Study report on individuals meeting outlier criteria or on "individual subject changes" on laboratory*

parameters such as Section 3.2.1 on page 160). Concomitant medications reported at baseline: amfebutamone hydrochloride 400 mg and lisinopril 10 mg/day.

*One subject (*500853) *was an ADO in Study -305 due to* ***elevated liver enzyme levels of up to 5 times the ULN on ALT on Day 14 that remained elevated through Day 19*** *of treatment (over 4 times ULN), along with elevations in AST and GGT. These events led to early discontinuation of Pal on Day 20. This subject was in a low dose group (3 mg Pal/day) and resolved about one week after treatment cessation. ALT increased up to 214 U/l (6-43 U/l within normal limits) and AST reached 76 U/l (11-36 WNL) and GGT was slightly elevated (72 U/l with 10-61 WNL).*

This ADO is likely to be drug-related *given no pre-existing condition or concomitant medications to explain these elevations and given resolution of these elevations upon dechallenge. It is noteworthy that this subject was in the lowest dose Pal group (only 3 mg/day). Therefore, it is possible that an unidentified underlying condition may have at least in part contributed to the elevations in LFTs.*

A copy of the narrative of the above subject and of others are provided in the latter part of this subsection.

The following provides more information on previously mentioned subjects who had baseline LFT abnormalities who were ADOs due to abnormal LFTs:

Study -303 describes 3 Pal subjects (201684, 201518 and 201445) who were ADOs due to non-serious liver-related events (occurred in 1 subject in each of the following Pal groups: 3 mg, 6 mg and 12 mg groups). All three subjects had abnormal LFTs (liver enzyme levels) at baseline and/or screening assessments and all three showed a further elevation or similar abnormal levels during DB Pal treatment that resulted in early treatment cessation. One of these subjects also had "fever" and "bronchial process." LFT elevations in this subject (201518) and subject 201445 did not exceed 3 times the upper limit of normal and one sucject was discintued on Day 1 of the DB phase.

Among the above 3 subjects (ADOs) with abnormal baseline LFTs, subject 201684 had the most remarkable LFT increases from approximately 2 times the ULN on ALT and AST at baseline to approximately 10 times the ULN on ALT and approximately 5 times the ULN on AST (GGT<2 times the ULN) on Day 17 of treatment (6 mg/day of Pal). This subject was on risperidone prior to the study (Day -4). A copy of the narrative is provided below and the following summarizes findings. Study drug was discontinued on Day 24 as levels remained high and LFTs started to decrease from previous values on Day 25. This subject was a 22 year old female subject who had abnormal levels at baseline but had no remarkable history that would explain her abnormal LFTs (as described on page 136 of the CSR). Clearly from the baseline values this subject had a pre-existing and undiagnosed condition. Yet these elevations could have been exacerbated by Pal treatment as suggested by decreasing levels upon treatment cessation and she was receiving Risperidone prior to the study and until Day -4.

Copies of Narratives of a few of the above subjects are provided below, so as to provide some more detail of the progression of the events and diagnostic work-up if any (of which some of the examples below also provide the investigator's or other clinical interpretations of which some may differ from the above interpretation by the undersigned reviewer). Key events described in these narratives were previously discussed above.

Although this subject was only receiving 3 mg Pal daily Pal-induced elevations in LFTs is suspected:

Subject 500853 (paliperidone; preferred term: hepatic enzymes increased;
[redacted]) was a 27-year-old man with a diagnosis of schizophrenia, undifferentiated type. The medical history and screening physical examination were normal; no history was reported of hepatic disorder or alcoholism. The subject discontinued haloperidol 7.5 mg/day, orphenadrine 100 mg/day; rescue medication lorazepam 1 mg/day was given only on Day -5. No concomitant medications were reported at baseline. At screening Day -2, laboratory values were unremarkable; the baseline (Day-1) laboratory values were normal. The hepatic enzymes at screening and baseline were within normal limits.
On Day 14 while receiving paliperidone 3 mg/day, *hepatic enzymes increased* (increased liver enzymes-verbatim) were reported as an adverse event.
Elevations were present in the following hepatic enzymes: alanine aminotransferase (ALT) 214 U/L (reference: 6-43 U/L), aspartate aminotransferase (AST) 71 U/L (reference: 11-36 U/L), and gamma glutamyl transpeptidase (GGT) 72 U/L (reference range 10-61 U/L).
On Day 19 the ALT was 171 U/L, the AST was 76 U/L, and the GGT was 58 U/L (within normal limits). On Day 27 (post study Day 7), the ALT remained elevated at 44 U/L, the AST was normal at 23 U/L and the GGT at 40 U/L was within normal limits.
Study medication was discontinued on Day 20 due to the increased liver enzymes, which resolved in 25 days. The investigator considered the increased liver enzymes to be moderate in severity and very likely related to study medication.
The subject received paliperidone 3 mg/day for 20 days and was withdrawn from the study on Day 20 due to the increased liver enzymes.
The ALT, AST and GGT were elevated at Day 14. The GGT returned to normal on Day 19, while the ALT and AST were further elevated. The subject was withdrawn from the study on Day 20 due to the increased liver enzymes. The AST returned to normal on Day 27 and the ALT remained elevated. As increased hepatic enzymes have been reported with the use of paliperidone, the sponsor considered that a causal relationship between the elevated hepatic enzymes and the use of the study medication in this subject cannot be excluded.

The following subject was previously described as having abnormal baseline LFTs but showed greater elevations on Pal:

"Subject 201684 (paliperidone; preferred term: hepatic enzymes increased;
[redacted]) was a 22-year-old white woman with a diagnosis of

paranoid schizophrenia. The medical history and screening physical examination were non-contributory to the adverse event. There was no history of hepatic disorder. The subject discontinued risperidone 2 mg/day on Day -4. Diazepam 10 to 15 mg/day was given as a rescue medication from Day 1 through Day 10. At screening, laboratory values were unremarkable for the relevant parameters; hepatic enzymes were within normal limits.
At baseline, elevations were noted for alanine aminotransferase (ALT 71 U/L; reference: 6 to 34 U/L) and aspartate aminotransferase (AST 50 U/L; reference: 9 to 34 U/L). Despite the ALT elevations twice the upper limit of normal (a protocol violation), the subject entered the study.
On Day 17, while receiving paliperidone 6 mg/day, an adverse event of *hepatic enzymes increased* (liver enzymes increase-verbatim) was reported. At this time, ALT was 376 U/L, AST was 164 U/L, gamma-glutamyltransferase (GGT) was 60 U/L (reference: 4 to 49 U/L), and lactic dehydrogenase (LDH) was 228 U/L (reference: 53 to 234 U/L). Study medication was unchanged.
On Day 22, ALT was 320 U/L, AST 164 U/L, GGT 59 U/L, and LDH 232 U/L. Study medication was discontinued on Day 24 as a result of the increased liver enzymes.
On Day 25, ALT was 230 U/L, AST 80 U/L, GGT 54 U/L, and LDH 173 U/L. The investigator assessed the liver enzymes increase as moderate in severity and doubtfully related to the study medication. The adverse event was ongoing at the time of study discontinuation.
The subject received paliperidone 6 mg/day for 24 days and was withdrawn from the study on Day 25 due to this adverse event.
ER OROS Paliperidone: MODULE 2.7 Clinical Summary; 2.7.4 Clinical Safety
The adverse event, "hepatic enzymes increased" was reported on Day 17. However, ALT and AST were increased at baseline. Although increased hepatic enzymes have been reported with the use of paliperidone, the sponsor considered a causal relationship between the adverse event, "hepatic enzymes increased", and the use of the study medication in this subject unlikely."

O. Remarkable Glucose-Related SAEs.

It is noteworthy that elevated levels of glucose, which is expected for the drug class (as described in labeling of approved atypical antipsychotic agents). Many of the patients with elevated glucose levels or other related abnormal laboratory measures (e.g. elevated insulin levels) had pre-existing diabetes mellitus or abnormal glucose (and insulin levels in some paitents) at baseline. Some patients had risk factors for diabetes mellitus (e.g. obesity). Most events of hyperglycemia resolved in these patients (e.g. after cessation of Pal).

Although hyperglycemia is already described in proposed labeling (as is the standard for drug class labeling for this drug class) it may be informative to ask the sponsor about any cases where hyperglycemia did not resolve upon dechallenge. Yet it may still be difficult to interpret results since some patients may have had undiagnosed diabetes or undetected diabetes prior to treatment which would be difficult to determine in retrospect.

Weight gain is known to be associated with this drug class and was observed with Pal which can increase risk for diabetes.

The following subjects were some examples of SAEs due to hyperglycemia and/or other events that were found upon review of some of the short-term trial CSRs:
The CSR of Study -305 describes the following SAEs in Pal subjects. SAEs of diabetes mellitus and hypoglycemia were reported in a subject (S501122). This subject subsequently developed SAEs of "renal failure acute" and "GI hemorrhage" which were reported on Day 40 of the DB phase (in the 9 mg Pal group) who was hospitalized. This 45 year old female subject had a history of diabetes, hypertension and was overweight at baseline. She also had elevated OGTT glucose levels at baseline, as well as elevated cholesterol and triglyceride levels. While a role of Pal is possible, this subject had pre-existing conditions that at least contributed to these events.

S501300 had hyperglycemia as an SAE and ADO on Day 11 of the DB Phase who was obese, 36 year old male and had increased appetite and weight gain during 15 mg Pal daily. This subject had elevated glucose and insulin levels at screening. Hyperglycemia resolved after cessation of treatment.

See section 7.1.4.13 for a special search for glucose related AEs conducted by the sponsor.

P. SAEs of Hyponatremia or "Water Intoxication"

SAEs of hyponatremia were reported in a few subjects in both placebo and Pal groups.

The Pal subject in Study -305 with this SAE (501136) had a previous history of seizure due to hyponatremia and was reported to have "water intoxication" on Day 18 on Day 18 of 9 mg/day Pal that resolved with treatment within 3 days. Study drug was discontinued on Day 19 due to extrapyramidal related AEs. Electrolyte levels were normal in this subject except for a low potassium on Day 20.

The following subject was found in a line listing of OL subjects in the 120-Day SUR who was previously listed under Subsection I on Seizures:

- *Subject 500108 (SAE and ADO): had convulsion reported, hyponatermia, psychogenic polydipsia, aspiration pneumonitis and exacerbation of schizophrenia reported. Psychogenic polydipsia has been reported in this patient population which can lead to these other events of hyponatremia, convulsion and aspiration pneumonitis.*

Q. SAEs of Duodenal Perforation or Gastrointestical Hemorrhage

Because of the formulation (OROS) it is important to describe any potential cases of duodenal perforation. See below.

1 SAE of Duodenal Perforation and 1 SAE of Gastrointestinal Hemorhage in a 6 mg and 9 mg Pal Subject, respectively were reported with subject descriptions as follows in which the etiology of these events are not clear:

- *See the description of subject 501122 in Study -305 (in the 9 mg Pal group) above who had diabetes mellitus who had SAEs of "diabetes mellitus," "renal failure acute," and "GI hemorrhage." This subject had a history of pre-existing conditions (diabetes mellitus, hypertension, overweight, among other conditions) that can lead to these type of events, although the role of the study drug is possible given the events of hyperglycemia known to be associated with this drug class as described in labeling of approved drugs. The etiology of GI hemorrhage is not clear based on the sponsor's description found in the CSR. This subject had multiple conditions that complicated the clinical picture.*
- *The CSR of Study 303 describes one Pal subject (201333) with "ruptured duodenum" on Day 37 of 6 mg Pal treatment (in a 47 year old male) that required surgery and required early study withdrawal. This subject is not described as having any concomitant medications or any remarkable medical conditions or clinical abnormalities. Therefore the etiology of this serious and remarkable clinical event cannot be determined.*

The potential role of the OROS formulation is unclear in the above cases. The former subject had multiple serious medical conditions and one might suspect that this patient had a pre-existing undiagnosed GI disorder (obese, diabetes, renal failure, and others). However, the OROS capsules may have exacerbated and undiagnosed underlying condition. The latter subject is less clear.

The other subject is less clear, but could be an isolated case. Labeling should include standard language as was used for Concerta® as follows (copied from approved labeling) but should also include a comment on the total number of subjects in all clinical trials in the development program who had any evidence of GI rupture or GI hemorrhage and described the number of days and daily dose (with number of capsules received daily), which would be the above subject.

"Potential for Gastrointestinal Obstruction

Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients)."

See the last section of this review for recommendations.

R. Anaphylactic Reaction and Steven Johnson's Syndrome

Only 1 SAE of anyphylactic reaction was reported but was treatable with diphenydramine but the subject had a recurrence, so the study drug had to be discontinued. The sponsor did not describe any cases of Steven Johnson's syndrome that could be found in in-text sections or reported as SAEs or ADOs..

S. Thrombocytopenia Cases:

A clinically unremarkable numerical mean decrease in platelet count observed almost consistently in all trials. There were not ADOs or SAEs of thrombocytopenia that could be found in Phase III trials except for the following that appeared to have an underlying etiology. Although a bone marrow biopsy was not performed on this subject and other key diagnostic test were not mentioned to confirm the diagnosis. This subject is described below.

100847 Study -301 as on page 1824 of SCS: This subject is a 41 year old who developed low platelet count (as low as 80, 000/mm$^{3)}$ days after starting OL Pal during the stabilization phase if study -301 (Day 15 in this study phase and Day 71 in the study involving OL Pal). The subject was receiving 12 mg of Pal daily (as described in the narrative provided in the Safety update report submission under this NDA). This SAE was worked up by a hematologist. The subject also had high reticulocyte count, megaloblastic and macrocytic anemia and decreased WBC from 9400 at baseline to 5400 during OL Pal treatment (hematology values on all parameters including platelet count were generally normal at baseline. He was not receiving concomitant medications and his hematology work-up was negative (no jaundice, hepatomegaly or splenamegaly, no schistocytes on peripheral smear or elevated bilirubin and no lymphadenopathy or evidence on physical examination for cancer. Bone marrow and B12 and folate levels were not obtained but the patient was treated with multiple vitamins (iron, folate, and others) and thyroid extract. Hematology parameters showed improviement with this treatment as the patient was continued on OL Pal with the dose titrated up to 12 mg daily. Platelet count increased to 260,000. mm^3 on a date that appears to be after multivitamin treatment was initiated and whiel the patient was continued on Pal. The patient also had elevated LDH. The hematologist suspected a nutritional deficiency in this 54 kg male subject with schizophrenia as follows (as copied from the CIOMS Report on this subject on page 2088 of the SCS):

> A hematoglist's evaluation revealed the appetite of the patient increased along with behavioral improvement while on study medication. Subsequently the subject started complaining of lethargy, weakness, anorexia and shortness of breath. A complete blood count showed mild pancytopenia and elevated LDH. The pancytopenia subsequently improved after receiving B12 injections along with folic acid 1 mg intramuscularly for 10 days. The hematologist also reported

"The peripheral blood picture, pancytopenia, elevated LDH and prompt response to B12 and folate is consistent with B12/folate deficiency. I feel this is nutritional B12/folate deficiency. In India, this is a very common problem, hence B12/folate levels and bone marrow is not routinely performed in all cases. It is done only if the patient does not respond to B12 and folate. I do not feel this is drug induced marrow suppression or drug induced impaired absorption of B12/folate. The development of B12/folate deficiency and commencement of the drug is purely coincidental".

T. Miscellanious SAEs or ADOs

The following is an additional remarkable SAE to which the etiology is unknown that was found by the undersigned reviewer (that did not fall under previous categories):

- *Subject 201422: This 56 year old female is described because she had an **SAE of "traumatic hematoma"** that required **"subcranial evacuation"** and was associated with "complications." This SAE was reported **on Day 255 of OL Pal (9 mg/day)** and **lead to an ADO**, as well as hospitalization and surgical intervention. She also had the SAE of "schizophrenia aggravated" that required continued hospitalization after she recovred "with uspecified seqeuelea on Day 269." This subject had **AEs of "arterial hypertension (3 times)" and "increase weight" during OL treatment.** She had received placebo during the DB 6-week lead-in study. Without additional information at least a role of Pal is suspected.*

Additional SAEs or ADOs from Phase I Trials

The following are noted since they may suggest a new finding not previously described and not described in drug class labeling of approved antipsychotic agents.

Narrative for Discontinuation Due to Adverse Event
R076477-SCH-1010
CRF ID: 100040
Country: Romania
Study medication: ER OROS paliperidone
Subject 100040 (dystonia), a 34-year-old white man with residual-type schizophrenia and an otherwise unremarkable medical history, was randomized to the ER OROS paliperidone group. His baseline PANSS score was 50 and the CGI–S indicated mild disease severity. Prior to the study, he was taking clozapine 200 mg once daily which was stopped on Day -5. The subject presented with mild diarrhea on Day -1 which resolved the same day with furazolidone treatment. On Day 2 of the study, the subject experienced mild oculogyric crisis and moderate severity **laryngeo-pharyngeal dystonia** which resolved the same day after treatment with diazepam and trihexyphenidyl. The subject withdrew from the study on Day 2 due to the adverse events and clozapine therapy was resumed on Day 4 for treatment of psychosis. At baseline (Day -10), his serum chloride level was 107 mmol/L (normal range: 94 and

112 mmol/L). By Day 5, the value had increased to 113 mmol/L. A concurrent creatine kinase level was also elevated (607 U/L; normal range: 18-198 U/L). With exception of low serum cholesterol values (3.02 and 3.64 mmol/L; normal range: 3.88-6.83 mmol/L), all other serum chemistry values were within normal limits. No follow-up laboratory information is available.

7.1.4 Other Search Strategies

The following subsections are special search strategies conducted by the sponsor.

7.1.4.1. Sponsor's Results of AEs of "Common" AEs of "Interest"

The sponsor analyzed common AEs of "interest" of which findings are summarized in subsections below. The sponsor conducted this analyses on completed short term Phase III trials (Studies -303, -304, -305, short-term, placebo-controlled, fixed, parallel group 6-week trials using multiple dose-levels) and on the ongoing OL extension trials (-702, -703, -704, -705). The sponsor also provides results from the elderly short-term, flexible-dose (3 to 12 mg/day), placebo controlled Phase III trial, Study -302.

All results described in this section including any descriptions of related SAEs and ADOs are using a 5/31/05 cut-off date for ongoing studies (the longterm OL studies).

An analyses of AEs of "interest" were not conducted for the ongoing placebo controlled "prevention of recurrence" study (-301) and for the ongoing OL extension trial (-701 of which Study -301 is the lead-in study).

Reviewer Comment and Caveat to Results Described in Subsections 7.1.4.1-12.
Please refer to previous sections of this review for a description of additional cases found by the undersigned reviewer (primarily provided in Section 7.1.3.3 of this review). Also see previous comments on questions that the sponsor was asked to clarify on other cases (see Attachment 1 and Section 7.2.8).

The sponsor has responded to some of questions about potentially clinically remarkable subjects (e.g. listing all subject with syncope, questions about capturing subjects with suicidality)), while responses to other questions relevant to finding potentially clinically remarkable subjects are pending at the time of this writing. Responses received late in this review cycle have not yet been reviewed (see Section 4.1 for a listing and Attachment 1 for questions asked).

Refer to the last section of this review for more comments and recommendations.

One additional comment about results provided below is that the results of ongoing OL trials are difficult to interpret. Therefore, the OL trial results are generally not described in this review, unless the undersigned reviewer found results that might suggest a new signal not was observed in the short-term trials.

7.1.4.2. Search for Tachycardia-related AEs

Reviewer Comments. *Results are similar to that described in the subsection below of "Common AEs" (section 7.1.5) in which a drug-related signal for tachycardia was found.*

The following summarize the sponsor's results:

- *An incidence of 9 to 14% of tachycardia was observed in paliperidone groups (3, 6, 9, 12 and 15 mg daily dose-levels) compared to 7% in the placebo group in fixed dose, placebo controlled, parallel group, short term Phase III trials of almost all non-elderly patients (included AEs of increased heart rate, sinus tachycardia, tachycardia and tachycardia paroxysm).*
- *The elderly short-term Phase III Trial (-302) showed a 16% incidence of tachycardia in Pal subjects (flexible daily dose of 3 to 12 mg) compared to 0 placebo subjects.*
- *The sponsor also conducted "life table" analyses of AEs of interest, including tachycardia. Based on these analyses the sponsor reports that tachycardia was reported by most subjects within 2 weeks of treatment in short-term DB Phase III trials and within the first month of OL treatment in the OL extension trials.*

7.1.4.3. Search for Orthostatic Hypotension-related AEs

The incidence of orthostatic hypotension reported as an AE and of outliers on vital sign parameters (meeting criteria for orthostatic hypotension) are described under appropriate sections in this review (refer to Sections 7.1.5 and 7.1.8, respectively).

Reviewer Comment. *Orthostatic hypotension is known as an adverse effect of atypical antipsychotic drugs and is generally described under Precautions in approved drugs in this drug class.*

It is noteworthy that orthostatic hypotension as defined by objective vital measures occurs with a greater incidence and a greater difference in the incidence between Paliperidone and placebo groups (as high as 11% in the high-dose 15 mg group compared to only 4% of placebo subjects) than the incidence when orthostatic hypotension is reported as an AE (4% in the 15 mg compared to 1% placebo). This observation may suggest that many subjects meeting outlier criteria for orthostatic hypotension did not have symptoms and were therefore not considered by investigators to have a clinically significant event, such that the event was not reported as an AE.

The sponsor also describes results of a safety pharmacology Phase I study (-SCH-101) but since this study did not include a placebo group results are difficult to interpret. It is noteworthy that the incidence of orthostatic hypotension AEs that were elicited upon direct inquiry of the subjects (55% and 79% for the OROS and IR treatment conditions) were higher than AEs reported by the investigator (28% and 56% for each respective treatment condition). A greater incidence observed upon direct inquiry versus reported as an AE is not surprising to the undersigned

reviewer given that this observation has also been reported among placebo subjects in some past trials of other drugs that used a placebo controlled study design.

The results from the fixed dose, short-term Phase III dataset also shows at least trends for a dose-dependent effect with a greater incidence at higher dose-levels compared to lower dose-levels.

See Section 7.1.3.3 for potentially clinically remarkable subjects and section 7.1.8 for vital sign results.

Results of dose-dependent and time-dependent effects on the basis of vital sign results for orthostatic changes are discussed in Section 7.18 of this review.

See recommendations for labeling and further comment under the last section of this review.

7.1.4.4. Search for "Proarrythmic" Potential AEs

The incidence of "proarrythmic" related AEs involved a search for AEs of seizure, syncope, ventricular fibrillation and flutter, ventricular tachycardia, torsade de pointes and AEs "consistent with sudden death." The sponsor explains that these terms were selected in accordance with ICH E14 (a guidance document for evaluation potential QT prolongation effects).

The following outlines results of the short-term Phase III trial safety dataset:

- No Paliperidone subjects had sudden death related AEs.
- Seizures (convulsion or grand mal convulsion were reported in one 12 mg Pal subject (<1% in this 12 mg group) and one 6 mg Pal subject (<1%) and in no other treatment groups (including 0 out of 355 Placebo subjects and 0 subjects in the 3 mg, 9 mg and 15 mg Pal groups with a total of 286 subjects in these 3 Pal groups).
- Syncope was reported in 1 subject (less than 1% of subjects) in each treatment group including the placebo group (generally 1-3 subjects per treatment group of 127 to 355 subjects/group).

The sponsor had ECG data of all of the above subjects reviewed. The sponsor had vital sign data reviewed for subjects with syncope. The following observations were described in the SCS based on this review of ECG and vital sign data from these subjects:

- None of the 10 Pal subjects had QTcLD values of over 450 msec or an increase from baseline of greater than 60 msec at time-points near or at the time of the AE.
- Among the 8 Pal subjects with syncope, none had orthostatic hypotension based on postural vital sign data but 2 of these 8 subjects had the following abnormal vital signs:
  - Subject 300649 in the 6 mg group was a 36 year old female a standing HR of 120 bpm, supine BP of 90/50 mmHg. That day she had AEs of syncope, diaphoresis, hypoglycemia and dizziness (Day 2) which spontaneously resolved as she continued in the study.

- Subject 502318 in the 3 mg group was a 40 year old women with syncope and hypotension at baseline and on Day 2 (standing BP of 100-70).

No Pal subjects of the elderly Phase III trial, -302 had "proarrhythmic" related AEs (out of 76 total Pal subjects compared to 2 out of 38 placebo subjects (5%) with a proarrhythmic related AE).

The OL dataset showed only 2 subjects out of over 1000 subjects with a proarrhythmic related AE (syncope in 1 subject and seizure in another) in these Pal OL extension ongoing trials. These 2 subjects did not have a QTcLD of over 450 msec at or near the time of the AE or an increase by over 60 msec and vital signs were within normal limits in the subject with syncope (vital sign data was reviewed by the sponsor in subjects with syncope).

Reviewer Comment. *It is not clear from the description found in the SCS why the above OL subjects had syncope and seizure and the nature of these events is also unclear. A subject number for these subjects cannot be found.*

See Section 7.1.3.3 of this review for descriptions of additional subjects, including a subject with SAEs of hypotension and dizziness and had AEs of syncope and bradycardia. Holter monitoring revealed episodes of "pauses" of up to 8 seconds long in one subject 300541 that was found in the CSR of Study -304.

The sponsor was asked about subjects with syncope in Phase III trials (as discussed in other sections of this review) and a response was recently received late in the review cycle (so will be reviewed at a later date, as previously discussed).

7.1.4.5. Search for Ischemia-related AEs

Only 2 Pal subjects out of over 900 Pal subjects (<1% in their respective Pal 6 mg and 12 mg treatment groups) had an ischemia related AE (myocardial ischemia in each subject), and none of the 355 placebo subjects had this type of AE (upon a review of AEs with MedRA terms listed in Appendix 2.7.4.3.11 of the SCS that were identified as ischemia related AEs, according to the sponsor).

One elderly Pal subject in the elderly Phase III trial (Study -302) had "acute coronary syndrome" (out of 76 Pal subjects) and no placebo subjects had an ischemia related AE (out of 38 subjects). The "acute coronary syndrome" was reported as an ADO and an SAE (refer to Section 7.1.2 on SAEs). It should be noted that 1 placebo subject had "cardiac arrest" reported (refer to Section 7.1.2 on SAEs).

Seven out of 1167 (1%) of OL subjects had ischemia related AEs in the OL extension trials in which these subjects were reported as having an ADO and/or SAE due to an ischemia-related

AE. 5 of these 7 subjects had cardiac-related AEs of ischemia. The remaining 2 subjects had stroke-related AEs of ischemia ("ischemic stroke" or "transient ischemic attack").

Reviewer Comment. *The incidence of the above events are not unexpected for the study population. Refer to Section 7.1.3.3 of additional individual subjects with ischemia related events that were found upon review of CSRs of the three pivotal Phase III trials that were not found in the in-text sections of SCS including the section on ischemia related events.*

7.1.4.6. Search for Suicidality-related AEs.

Reviewer comment. *Based on results described below the incidence of suicidality is generally expected for the study population and Pal treatment groups showed a similar incidence to placebo in the pooled dataset from short term non-elderly Phase III trials, except that the high dose Pal group (15 mg) showed an incidence of 3% compared to 1% of placebo and almost all lower dose Pal groups (except the 3 mg group had an incidence of 2%). It is difficult to determine if this finding is a real finding versus an artifact (e.g. due to multiple group comparisons on multiple dependent errors resulting in a Type I error). However, since the greatest incidence was observed in the highest dose group and since there is only one dataset of placebo controlled, fixed dose trials with only one study using this high dose-level, then this result should be taken as a possible true positive finding at this time. The sponsor conducted a review of CRFs of SAEs (CIOMS forms, as described later) and found CRFs of subjects in which the investigator had comments related to suicidality but did not report an AE of suicidality. Upon inquiry by the sponsor the investigators who had these particular subjects verified they "judged that no suicidality-related AE should be recorded."*

The sponsor summary table is shown below.

Table 40: Treatment-Emergent Suicidality Adverse Events By MedDRA Preferred Term - Double-Blind Phase
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

Suicidality Group Dictionary-derived Term	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) N (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Olanzapine 10 mg (N=364) n (%)
Total no. subjects with suicidality-related AE	5 (1)	2 (2)	2 (1)	2 (1)	1 (<1)	3 (3)	5 (1)
Suicidality	5 (1)	2 (2)	2 (1)	2 (1)	1 (<1)	3 (3)	5 (1)
Suicidal ideation	4 (1)	2 (2)	2 (1)	1 (<1)	1 (<1)	3 (3)	3 (1)
Suicide attempt	1 (<1)	0	0	1 (<1)	0	0	2 (1)

It is important to note that the 10 Pal subjects with suicidality AEs in the short-term Phase III trial dataset had no history of suicidal ideation or suicide attempts. Yet, none of the placebo subjects of these trials that had suicidality who had a positive history for suicidality (as found upon review of the CSRs of these trials). Perhaps this reflects the subjects found by the sponsor that were not captured in the results that included some subjects with suicidality that was

believed to be due to the overall condition (e.g. were reported as SAEs due to "exacerbation of schizophrenia") as described in more detail below (also see Section 7.2.8 of this review).

The results of the OL trials are difficult to interpret since there was no placebo control group employed. However the overall incidence of suicidality (3% or less) in the Paliperidone treatment subgroups is not unexpected for this study population (based on the duration of treatment at the time the data were analyzed in these ongoing trials). 6 additional subjects in OL trials had suicidality described in the CRFs (according to the sponsor) but were not reported as having suicidality related AEs since the investigator consider the events as part of an exacerbation of their psychotic disorder and were reported as such. Even if these 6 additional subjects were reported as having suicidal related AEs and were counted as such, the incidence of suicidal related AEs in the OL subjects (a total of 31 subjects out of over 1100 total subjects, 2.8% is well within the expected incidence of suicidality for this study population).

The Safety Alert forms reviewed (CIOMS reports) by the sponsor's personnel revealed some subjects were found to have comments of suicidality in their CIOMS reports (but not reported as suicidal as an AE or separate SAE term). Upon inquiry with the investigator by the sponsor's personnel, these subjects were considered by the investigator to either not have suicidality or were subjects with suicidality that was believed to be part of the their overall clinical condition (and suicidality was not reported as an AE or SAE), as described in more detail under Section 7.2.8 of this review. Refer to Section 7.2.8 of potential concerns related to these findings. Despite these concerns the overall interpretation of the sponsor's results do not appear to be impacted (e.g. in favor of Pal over Placebo) with respect to a potential suicidality signal. The cases that the sponsor identified by a review CIOMS forms as being uncaptured included placebo, as well as Pal subjects and the number of subjects was small enough such that if these cases had been included in the sponsor results, then the overall interpretation of the results would not have been altered (e.g. the 15 mg group would still have a similar overall higher numerical incidence compared to placebo subjects).

See the final section of this review for further comment.

Results of the sponsor's analysis on suicidality events are described in more detail, below.

The completed short-term fixed-dose Phase III trials of almost all non-elderly subjects (pooled dataset) showed an incidence of 1% or less in placebo and paliperidone groups while a 3% incidence was reported in the high dose group (15 mg), while the 3 mg (low dose) group showed an incidence of 2%. Olanzapine group showed an incidence of 1%. Suicide attempt was only reported in 1 placebo subject, 1 9 mg Pal subject and in 2 olanzapine subjects (each of these groups had an incidence of 1% or less).

Methods of the sponsor's analyses on suicidality related events are described in more detail below.

The following describes the sponsor methods, but also provides details on some subjects that had comments of suicidality in the subject's CRF were not included in the sponsor's enumeration of suicidal-related cases (only CIOMS Safety Alert forms used for reporting SAEs) were reviewed by the clinical team for comments related to suicidality in which suicidality was not reported as an AE or SAE. In summary these cases were excluded because the investigator either "denied suicidality" or "reported the symptom as part of [the] overall clinical condition" such that suicidal ideation was not reported as an AE or as an SAE (but instead another SAE term was used such as exacerbation of schizophrenia for reporting the subject).

The sponsor determined the incidence of "suicide-related" AEs coded under MedRA preferred terms of completed suicide, suicidal ideation and suicide attempt (which were to be reported as SAEs). Note that these results likely reflect events as of the May 31, 2005 cut-off date. However, additional SAEs and deaths related to suicidality were reported in some trials after the 5/31/05 cut-off date but before the 8/31/05 cut-off date (used for deaths and SAEs and in some studies ADOs, of ongoing trials).

> "AEs coded under MedRA preferred terms related to suicidality were analyzed, as described in the following on page 107 of the SCS (copied verbatim): Suicide-related adverse events—coded under MedDRA preferred terms of completed suicide, suicide attempt, and suicidal ideation—were examined. Suicidality-related adverse events were to be reported as serious adverse events. Investigator comments were reviewed to identify suicidality associated with any other adverse events that were coded under other (non-suicidality) MedDRA preferred terms, and that the investigator did not deem reportable as suicidality-related adverse events."

Upon inquiry about the above methods the sponsor indicated that their clinical team reviewed selected CRFs (of SAEs) as follows (copied verbatim from their 5/23/2006 response):

> "During the conduct of Studies R076477- SCH-302, R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305, each serious adverse event (SAE) was reviewed by the clinical team for references to *suicidality, aggression or agitation.* If any of these terms were included in the investigators description of an event and not included as a separate adverse event (AE) on the Case Report Form (CRF) a Data Clarification Form (DCF) was sent to the site asking whether this term should be reported as an AE. If the site indicated it should not be added as an AE, the reply from the site to the DCF was entered in the Comments section of the database."

The following table shows the subject numbers of the above reviewed CRFs and bolded subject numbers indicates which subjects were enumerated as having a suicidal-related AE (as provided in a 5/23/06 response to our inquiry). Note that Appendix 2.7.4.3.8.3.1 of the SCS, referenced below, lists subject numbers of CRFs reviewed and Table 40 (referenced in the footnote to the

table) was the table in the SCS showing the incidence of suicidality-related AEs in the short-term Phase III trial dataset:

Table 2: Subject Listing by Treatment Group for Subjects Included in Appendix 2.7.4.3.8.3.1 in the SCS for Pooled Double-Blind Studies (R076477- SCH-302, R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305)

Placebo	3mg	6mg	9mg	12mg	15mg	OLZ
300619	501329	300381	501339	201519	**500623**	**200028**
500405				300301	501295	300692
500447						300397
501270						500464
						500672

- Bolded = those included in the SCS Table 40 and in the appendix 2.7.4.3.8.3.1

Table 5: Subject Listing From Appendix 2.7.4.3.8.3.1 With Rationale for Non-Inclusion in Table 40 for Double-Blind Studies (R076477- SCH-302, R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305)

Subject #	Treatment Group	Included/Not Included in Table 40	Rationale if Not Included as an AE
200028	Olanzapine 10 mg	Included	
201519	ER OROS PAL 12 mg	Not Included	Investigator denied suicidality
300692	Olanzapine 10 mg	Not Included	Investigator denied suicidality
300381	ER OROS PAL 6 mg	Not Included	Investigator reported symptom as part of overall clinical condition
300301	ER OROS PAL 12 mg	Not Included	Investigator reported symptom as part of overall clinical condition
300397	Olanzapine 10 mg	Not Included	Investigator denied suicidality
300619	Placebo	Not Included	Investigator reported symptom as part of overall clinical condition
500405	Placebo	Included	
500447	Placebo	Not Included	Suicide occurred after subject left the study and was not reported as an AE. No details available on this event.
500464	Olanzapine 10 mg	Not Included	Investigator reported symptom as part of overall clinical condition
500672	Olanzapine 10 mg	Not Included	Investigator denied suicidality
500623	ER OROS PAL 15 mg	Included	
501295	ER OROS PAL 15 mg	Not Included	Investigator denied suicidality
501329	ER OROS PAL 3 mg	Not Included	Investigator denied suicidality
501270	Placebo	Not Included	Investigator reported symptom as part of overall clinical condition
501339	ER OROS Pal 9 mg	Not Included	Investigator reported symptom as part of overall clinical condition

Table 6: Subject Listing From Appendix 2.7.4.3.8.3.2 With Rationale for Non-Inclusion in Table 41 for Open-Label Extension Studies (R076477- SCH-701, R076477-SCH-702, R076477-SCH-703, R076477-SCH-704 and R076477-SCH-705)

Subject #	Treatment Group	Included/Not Included in Table 41	Rationale if Not Included as an AE
300453	Pali/Pali	Not Included	Investigator denied suicidality
300623	Olan/Pali	Not Included	Investigator denied suicidality
300493	Pali/Pali	Not Included	Investigator reported symptom as part of overall clinical condition
300494	Pali/Pali	Not Included	Investigator reported symptom as part of overall clinical condition
300579	Pali/Pali	Not Included	Investigator denied suicidality
300098	Pla/Pali	Included	
300518	Pali/Pali	Included	
500108	Pali/Pali	Not Included	Investigator denied suicidality
500303	Pali/Pali	Included	

The CRFs that were reviewed for any suicide related comments. However, it appears that only selected CRFs were reviewed based on an inquiry to the sponsor of the investigator as to why a suicide related AE was not reported in subjects with CRFs containing comments related to suicidality, the investigators verified that suicidality-related AEs should not be reported in these particular subjects (4 out of 393 placebo subjects, 6 out of 1039 paliperidone subjects and 4 our of 364 olanzapine subjects).

The largest treatment group difference between Pal and placebo group reported in the SCS (that excluded un-reported cases) was 3% in the 15 mg group compared to 1% in the placebo group. Yet none of the 15 mg Pal subjects were among cases of suicidality that were not captured in these results (this specifically pertains to subjects that had suicidality described in the CIOMS form but that the investigator believed it to be part of the overall condition and were not reported using a term of suicidality and were not captured in this database as a suicidal event). Furthermore, several placebo subjects were found to fall under the category of un-captured cases. Additionally, consider all cases identified by the sponsor as uncpatured cases independent of the reason for these cases not being reported as cases of suicidality (e.g. cases in which the investigator denied suicidality after being inquired about comments in the CIOMS). If all such cases were included in the sponsor's results, then only one 15 mg subject out of a total of 113 subjects would be added to their enumeration of suicidality related cases. Consequently, if this single subject were counted among suicidality cases in this 15 mg group then the incidence would have been 3.5% which is not substantially different from 3%. In conclusion, the cases identified as not being captured in the sponsor's results on suicidality would not have altered overall conclusions if they had been included in the results (based on results provided in a 6/15/06 N005).

See sections 7.2.8 and the final section of this review for further comments and recommendations.

7.1.4.7. Search for Aggression or Agitation Related AEs.

Reviewer Comment. *The sponsor's search for aggression and agitation MedRA preferred terms (aggression, hostility, homicidal ideation, agitation and psychomotor agitation) failed to show a greater incidence of these AEs in any given Paliperidone group (ranging from 3% to 7% in any given group) compared to placebo (10%) in the short-term Phase III trial dataset of almost all non-elderly subjects. Similar results were observed for each type of AE in the Phase III dataset, as well as for the elderly Phase III Study -302 (for aggression and agitation-related AEs combined, and for each individual AE). Results of OL trials are difficult to interpret, as previously discussed but the overall incidence of 8% and 3% in the less than 3 month and 3 month and over Pal subgroups are not unexpected for this patient population and given that these studies are longterm trials of up to one year. As previously discussed the sponsor's subgrouping of subjects by duration of treatment is not a subgrouping to reflect the onset of these AEs relative to dosing but rather indicate how long a given subject has been on treatment at the time that safety data were analyzed in these ongoing trials (using a 5/31/05 cut-off date).*

7.1.4.8. Search for Somnolence Related AE

Reviewer Comment.
The table below (copied from the SCS) shows at least trends for a greater incidence of somnolence in all Pal groups compared to placebo except for the lowest dose Pal group (3 mg group).

Table 66: Treatment-Emergent Adverse Events of Somnolence By MedDRA Preferred Term - Double-Blind Phase
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

Somnolence Group Dictionary-derived Term	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Olanzapine 10 mg (N=364) n (%)
Total no. subjects with somnolence-related AE	25 (7)	7 (6)	22 (9)	24 (10)	26 (11)	10 (9)	70 (19)
Somnolence	25 (7)	7 (6)	22 (9)	24 (10)	26 (11)	10 (9)	70 (19)
Hypersomnia	0	0	0	0	0	1 (1)	0
Lethargy	0	1 (1)	2 (1)	0	0	0	0
Sedation	13 (4)	1 (1)	12 (5)	8 (3)	15 (6)	2 (2)	24 (7)
Somnolence	12 (3)	6 (5)	8 (3)	17 (7)	11 (5)	7 (6)	47 (13)

Elderly subjects in Study -302 also showed a greater incidence of somnolence-related AEs (9%) in Pal subjects compared to placebo subjects (5%).

According to the sponsor, the above AEs in Pal subjects were not reported as SAEs or ADOs except for 3 subjects (each subject was in the 6 mg, 9 mg and 12 mg groups respectively) who were ADOs due to these AEs (refer to Section 7.1.3 on ADOs later in this review).

7.1.4.9. Search for Prolactin Related AEs

Reviewer Comments. *It is not clear to the undersigned reviewer if all AEs listed in the sponsor's summary table (below) were actually prolactin related AEs. However, the results described in the SCS are not unexpected for this study drug or for the drug class and labeling in approved drugs in this drug class include a description of the known effects of these drugs on prolactin levels under Precautions. However, labeling for Risperdol® states that the "clinical significance of elevated serum prolactin levels is unknown for most patients." Refer to the final section of this review for recommendations in describing results of AEs that may be prolactin related that were reported with a greater incidence (twice that of placebo) in the 2 highest daily dose-levels of Pal (12 and 15 mg) examined in the pooled, fixed-dose, Phase III trials and as described in the next paragraph, below.*

The incidence of subjects with any given AE identified by the sponsor as prolactin related (for the 3 Phase III short-term studies, pooled dataset) was 1% in the placebo group and in Pal groups at the lower dose-levels (3 mg, 6 mg and 9 mg), while the incidence was greater at the higher dose-level Pal groups of 12 mg (2%) and 15 mg (4%). These results are not shown in the summary table shown in this subsection (but were described in the SCS). Since the higher Pal dose-levels showed twice the incidence observed in lower-dose Pal groups and compared to the placebo group the results provide some evidence for a dose-dependent effect of Pal on these types of events. According to the sponsor, none of the prolactin-related AEs in the pooled Phase III short-term trial dataset were reported as SAEs and 1 AE was reported as an ADO (galactorrhea).

The following summary table was provided by the sponsor (prolactin-related AEs were not found by the sponsor for the elderly Study -302).

Table 58: Number of Subjects With Treatment-Emergent Potentially Prolactin Related Adverse Events by MedDRA Preferred Term and Sex
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Olanzapine 10 mg (N=364) n (%)
Male	235	81	137	152	148	73	245
Erectile dysfunction	1 (<1)	0	1 (1)	0	0	1 (1)	1 (<1)
Female	120	46	98	94	94	40	119
Amenorrhoea	0	0	1 (1)	1 (1)	0	0	1 (1)
Menstruation irregular	0	0	1 (1)	0	0	0	0
Both	355	127	235	246	242	113	364
Anorgasmia	0	0	0	1 (<1)	1 (<1)	1 (1)	0
Breast discharge	0	0	0	0	1 (<1)	0	0
Breast pain	0	0	0	0	0	1 (1)	0
Galactorrhoea	0	1 (1)	0	0	1 (<1)	1 (1)	1 (<1)
Hypertrophy breast/gynaecomastia	0	0	0	0	1 (<1)	0	0
Libido decreased	0	0	0	0	0	1 (1)	0
Loss of libido	0	0	0	0	1 (<1)	0	0
Sexual dysfunction	1 (<1)	0	0	0	0	0	0

Note: Percentages calculated with the number of subjects per sex as denominator.

Table 59: Treatment-Emergent Potentially Prolactin Related Adverse Events by MedDRA Preferred Term and Sex
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)
Male	64	73	97	278	74	84
Erectile dysfunction	1 (2)	0	0	4 (1)	0	4 (5)
Female	43	55	81	227	32	59
Amenorrhoea	0	2 (4)	1 (1)	7 (3)	0	1 (2)
Menstruation irregular	0	3 (5)	0	1 (<1)	0	1 (2)
Both	107	128	178	505	106	143
Anorgasmia	0	0	0	1 (<1)	0	0
Blood prolactin increased	0	1 (1)	0	1 (<1)	0	0
Breast pain	0	0	0	2 (<1)	0	0
Breast tenderness	0	0	0	1 (<1)	0	0
Galactorrhoea	0	1 (1)	0	4 (1)	0	1 (1)
Hyperprolactinaemia	0	1 (1)	0	0	0	0
Hypertrophy breast/gynaecomastia	0	0	0	2 (<1)	0	0
Libido decreased	0	0	0	1 (<1)	0	0
Loss of libido	0	0	0	1 (<1)	0	0
Sexual dysfunction	0	0	0	4 (1)	0	0

Note: Percentages calculated with the number of subjects per sex as denominator.

7.1.4.10. Search for Gastrointestinal Obstruction and Related AEs

Since Pal was given as "non-deformable" tablet (OROS formulation) the sponsor determine the incidence of AEs related to gastro-intestinal obstruction (GIO AEs, using MedRA terms listed in Appendix 2.7.4.3.11 in the SCS).

None of the subjects in any of the 4 short term, completed, Phase III trials or in the ongoing OL trials had a GIO AE.

Reviewer Comment.
The undersigned reviewer found one subject with an SAE of ruptured duodenum previously described under Section 7.1.3.3 of this review. A description of this subject could not be found in in-text sections of the SCS but was found in line listings and narratives in appendices to the SCS.

7.1.4.11. Search for Neuromuscular Malignant Syndrome Related AEs

Neuromuscular malignant syndrome (NMS) was not reported for any subjects in the completed Phase III trials (-302 through -305) or for the ongoing OL studies (-701 through -705). According to the sponsor, NMS and increased blood creatine phosphokinase (CPK) were reported for 1 subject (100057) in the ongoing "prevention of recurrence" trial, Study -301 after receiving 3 weeks of blinded study drug (remains blinded). While this 34 year old male's symptoms have resolved "at this time" his CPK remains elevated. NMS was not reported in any of the Phase I/II studies.

Reviewer Comment. *At least one additional subject considered by the undersigned as likely to have had AEs of NMS was previously described, along with the above subject 100057 under Section 7.1.3.3 of this review.*

See results on laboratory parameters later in this review showing inconsistent elevations in CPK in Phase III trials and results in Phase I trials suggesting a dose-dependent signal for elevated CPK in Phase I trials using the OROS Pal formulation.

Refer to the last section of this review for further comment and recommendations.

7.1.4.12. Search for Extrapyramidal Side Effect Related AEs

The following results were found in the SCS.

Table 45: Treatment-Emergent Extrapyramidal Symptom (EPS) Related Adverse Events (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

EPS Group Dictionary-derived Term	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) N (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Olanzapine 10 mg (N=364) n (%)
Total No. with any EPS-related adverse event	39 (11)	16 (13)	24 (10)	62 (25)	63 (26)	27 (24)	31 (9)
Dyskinesia	12 (3)	6 (5)	6 (3)	19 (8)	21 (9)	10 (9)	7 (2)
Dyskinesia	3 (1)	0	1 (<1)	1 (<1)	4 (2)	1 (1)	1 (<1)
Extrapyramidal disorder	8 (2)	6 (5)	5 (2)	17 (7)	18 (7)	9 (8)	6 (2)
Muscle twitching	1 (<1)	0	0	0	0	0	0
Tardive dyskinesia	0	0	0	1 (<1)	0	0	0
Dystonia	4 (1)	1 (1)	3 (1)	13 (5)	11 (5)	2 (2)	3 (1)
Dystonia	2 (1)	1 (1)	3 (1)	9 (4)	9 (4)	1 (1)	1 (<1)
Muscle spasms	1 (<1)	0	0	1 (<1)	2 (1)	1 (1)	1 (<1)
Oculogyration	0	0	0	5 (2)	0	0	0
Trismus	1 (<1)	0	0	0	0	0	1 (<1)
Hyperkinesia	14 (4)	5 (4)	7 (3)	20 (8)	24 (10)	11 (10)	8 (2)
Akathisia	14 (4)	5 (4)	7 (3)	20 (8)	23 (10)	11 (10)	7 (2)
Hyperkinesia	0	0	0	0	1 (<1)	0	0
Restless legs syndrome	0	0	0	0	0	0	1 (<1)
Parkinsonism	8 (2)	4 (3)	6 (3)	18 (7)	15 (6)	7 (6)	8 (2)
Bradykinesia	0	0	0	1 (<1)	0	0	0
Cogwheel rigidity	1 (<1)	0	0	0	0	1 (1)	0
Drooling	1 (<1)	0	2 (1)	1 (<1)	0	2 (2)	1 (<1)
Hypertonia	4 (1)	3 (2)	3 (1)	10 (4)	8 (3)	4 (4)	5 (1)
Hypokinesia	0	0	0	0	1 (<1)	0	0
Muscle rigidity	0	1 (1)	0	3 (1)	1 (<1)	0	0
Musculoskeletal stiffness	2 (1)	0	0	0	2 (1)	0	0
Parkinsonism	0	0	1 (<1)	5 (2)	3 (1)	2 (2)	2 (1)
Tremor	12 (3)	4 (3)	6 (3)	11 (4)	8 (3)	3 (3)	8 (2)
Tremor	12 (3)	4 (3)	6 (3)	11 (4)	8 (3)	3 (3)	8 (2)

Figure 2: Simpson-Angus Rating Scale (SAS): Change From Baseline to End Point
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

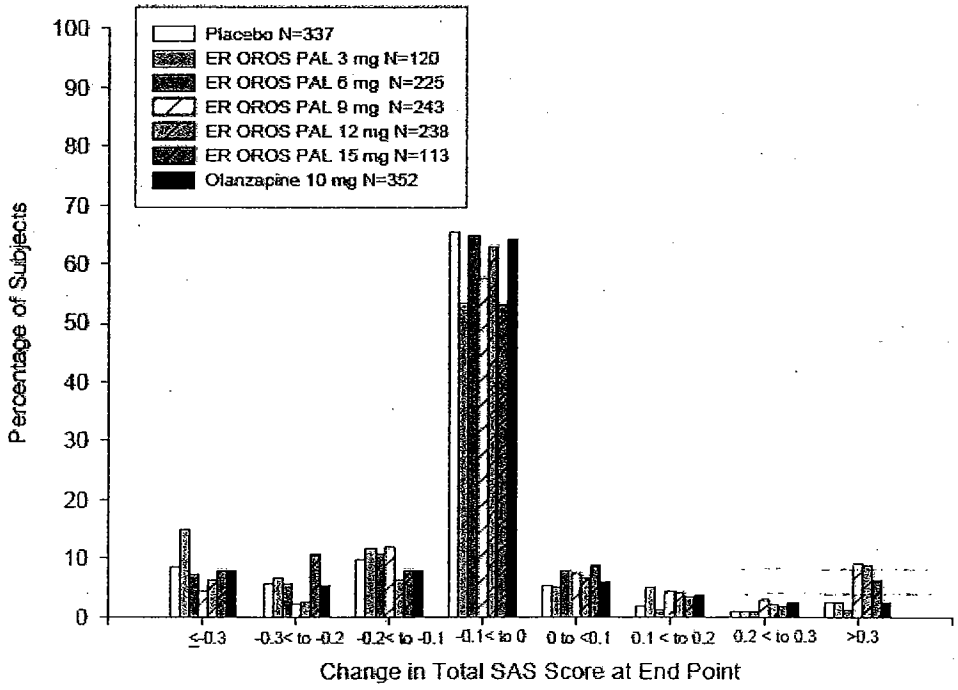
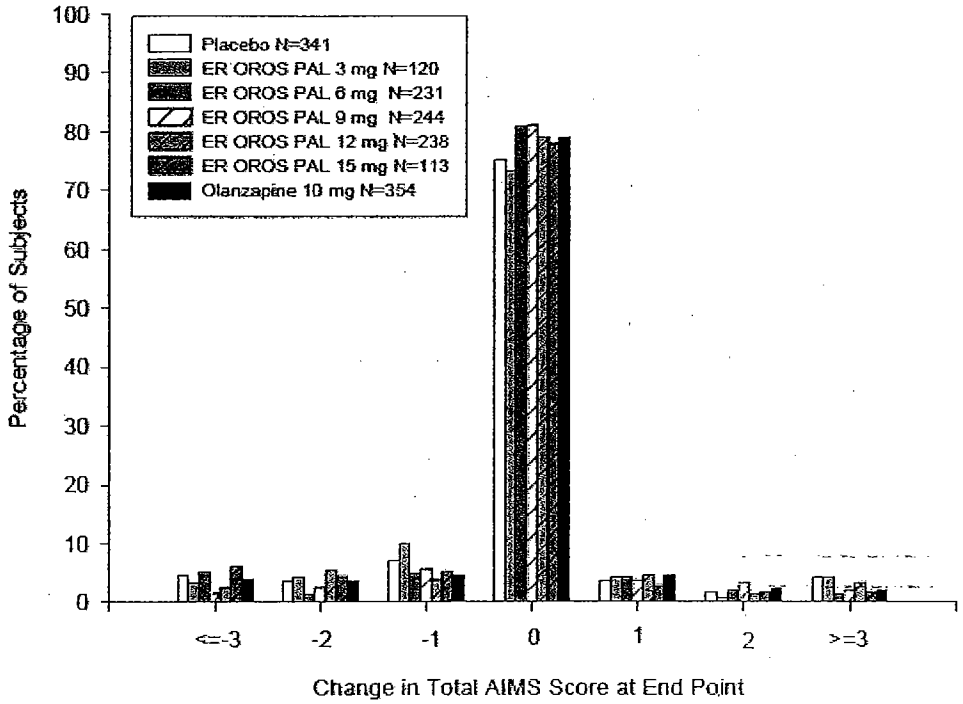


Table 46: Summary of BARS Global Clinical Rating Score at End Point
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

				ER OROS PAL				Olanzapine
	Placebo (N=355) n (%)	3 mg (N=127) N (%)	6 mg (N=235) n (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)	15 mg (N=113) n (%)	Total (N=963) n (%)	10 mg (N=364) n (%)
Global clinical rating of akathisia								
End point								
Absent	278 (81.0)	104 (85.2)	204 (87.9)	203 (83.2)	189 (79.1)	89 (78.8)	789 (83.1)	316 (88.5)
Questionable	43 (12.5)	10 (8.2)	18 (7.8)	23 (9.4)	29 (12.1)	15 (13.3)	95 (10.0)	25 (7.0)
Mild akathisia	14 (4.1)	7 (5.7)	6 (2.6)	15 (6.1)	14 (5.9)	8 (7.1)	50 (5.3)	13 (3.6)
Moderate akathisia	6 (1.7)	1 (0.8)	3 (1.3)	3 (1.2)	6 (2.5)	1 (0.9)	14 (1.5)	2 (0.6)
Marked akathisia	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)	1 (0.3)
Severe akathisia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)

Figure 3: Abnormal Involuntary Movement Scale (AIMS): Change From Baseline to End Point (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)



The following results on the incidence of concomitant medication (including antihistamine drugs) use for EPSE were also provided for each treatment group (for Phase III -303 through -305, combined) in the SCS:

- 3 mg Pal (14%)
- Pal 6 mg (13%)
- 9 mg Pal (22%),
- 12 mg Pal (24%),
- 15 mg Pal (21%)
- Placebo (14%)
- Olanzapine (12%).

7.1.4.13 Search for Glucose Related AEs

Reviewer Comment. *It is well known and is described under Precautions of Risperdol® and other drugs in this drug class, that hyperglycemia and diabetes mellitus has been reported in treated subjects such that the sponsor has not revealed any new or unexpected findings.*

In summary, the fixed dose, short-term Phase III dataset showed a 1% incidence in each treatment group (Pal groups, Olanzapine and placebo) except for 2% in the lowest dose Pal group (3 mg). Two SAEs are also described by the sponsor in this section of the SCS (on page 130) of Subject 501300 in the 15 mg group with no prior history of hyperglycemia who developed this event during treatment that resolved upon dechallenge (this subject was also an ADO due to this event). Subject 501122 in the 9 mg group had a history of diabetes mellitus who had AEs of "diabetes mellitus" and "hypoglycemia." While the former described subject was likely to have a drug-related event the events of the latter subject are less clear regarding their relationship to Pal treatment.

Open label trials failed to show any new remarkable findings. This dataset showed an incidence of 0% in most OL subgroups except for the > 3month Placebo (DB lead-in study treatment)/Paliperidone (OL treatment) subgroup (2%) and <1% in the > 3month Paliperidone/Paliperidone group.

7.1.5. Common Adverse Events

This section focuses on the incidence of common AEs which includes summary tables that were provided by the sponsor.

This section begins with a summary and interpretation of results as provided in the opinion of the undersigned reviewer (as denoted by italicized text). Summary tables of the incidence of common AEs follow thereafter (as provided by the sponsor that were primarily found in the SCS of the submission).

In accordance with the MAPP, results on the incidence of AEs on the basis of gender, age and ethnic subgroupings are provided under subsection 7.1.5.6.

Reviewer Comment and Summary. *The summary AE tables of completed Phase III trials of primarily non-elderly subjects (of pooled data from Studies -303, -304 and -305, shown in this section) reveal results that are expected (for at least one of the following reasons):*

- *Given the known effects of Risperidone*
- *Given the known Drug class or*
- *Given the known mechanism of action of the drug (at the receptor level) or*
- *Were findings that are expected for the study population.*

Some AEs failed to show consistent or remarkable evidence for a drug-related effect.

The following are notable or possible exceptions to the above conclusions (most of the following AEs occurred in at least 2% of subjects in a given Paliperidone group with at least twice the incidence observed in placebo and suggested a consistent drug-related effect based on the pattern of the incidence across dose-levels of Pal):

a) Cardiac related events, as follows.

- *Tachycardia or sinus (s) tachycardia. While some AEs could be tachycardia due to orthostatic hypotension (an expected event), one cannot assume that all events were due to this expected drug-related adverse effect. See a discussion of evidence for drug induced supine tachycardia described under the section on vital signs (section 7.1.8) and SAEs involving tachycardia that could not be explained by the presence of orthostatic hypotension.*
- *1° Atrioventricular block (AV block) occurred in 4.4% of 15 mg Pal subjects compared to 1.4% of placebo subjects which is an unexpected event. Note later in this review results on potential PR prolongation effects that appeared to be of a clinically unremarkable magnitude.*
- *QT prolongation is unexpected for the study drug but is observed to varying degress with other antipsychotic drugs of primarily other drug classes but has been reported with some atypical antipsychotic agents. QT prolongation (as an investigation AE) was reported with an incidence in the 3 mg, 12 and 15 mg Pal groups that was at least twice that of placebo subjects but was not common (most groups had an incidence of <2% with only the 3 mg group being the exception with an incidence of 2.4%).*

b) Suicidal ideation occurred in 2.7% of 15 mg Pal subjects compared to 1.1% of placebo subjects, 1.6% of 3 mg Pal subjects and less than 1% of subjects in each of the other Pal groups (6, 9 and 12 mg groups). Depression and anxiety or other potentially related psychiatric AEs did not show evidence for drug-related effects based on the incidence of these AEs shown in the sponsor's summary table, but sleep disorder did show drug-related effects on the incidence of this AE. See the results of the sponsor's special search strategy for AEs of suicidality described under Section 7.1.4 in this review.

c) The following infection-related or respiratory-related AEs shown an unexpectedly greater incidence in at least the 15 mg Pal group compared to placebo (and the incidence was at least twice that of placebo):

- *Upper respiratory tract infection and urinary tract infection in 3.5% and 2.7% of the 15 mg group, for each AE, respectively compared to 0.6% of placebo subjects (for each AE) and generally less than 1% of subjects given lower Pal dose-levels.*
- *Respiratory related AEs of cough occurred in approximately 2 or 3% of Pal subjects at each dose-level compared to 1.1% of placebo subjects, nasal congestion was reported in 3% of 15 mg Pal subjects compared to <1% in the lower dose Pal groups and in placebo subjects.*

Tachycardia, upper respiratory infection, coughing, rhinitis and other related AEs did show evidence of drug-related effects based on the incidence of these AEs in summary tables of Schizophrenia short term trials (used 10 and 16 mg daily dose-levels) and Bipolar short term trials (used 1-6 mg daily dose-levels) in approved labeling for Risperdol.®

While tachycardia is included in summary tables of adverse events in approved Risperdol® labeling, tachycardia is described in Risperdol® labeling as being associated with orthostatic hypotension under Precautions, similar to approved labeling for other antipsychotic drugs in

this drug class. However, refer to previous descriptions of SAEs and/or ADOs of tachycardia, independent of orthostatic hypotension under Sections 7.1.2 and 7.1.3.

Common AEs in the Elderly Phase III Trial (Study -302).
The placebo controlled elderly Phase III trial generally showed similar findings, in which the following unexpected findings to the undersigned are noted (see the above discussion of tachycardia as described in approved Risperdol® labeling):

- *Incidence of sinus tachycardia and tachycardia AEs were 0% in placebo (for each AE) compared to 5% of each AE in the Pal group.*
- *QT prolongation was reported in 7% of Pal subjects compared to 3% of placebo subjects.*
- *The following were observed in the elderly trial but not the sort-term Phase III trials that were primarily of non-elderly patients (the incidence of Pal and placebo groups are shown):*
  - *Hypertension (5%, 3%, respectively)*
  - *Hypotension (5%, 0%): one cannot assume that hypotension in these subjects was orthostatic hypotension.*
- *1° AV block in 3% (2 out of 76 Pal subjects) compared to 0 placebo subjects (out of 38 placebo subjects).*

Common AEs in OL Trials
Results of the longer term OL trials (-702 through-705) are difficult to interpret since there was not a placebo group. Also comparisons between results of subgroups on the basis of Pal exposure of 3 months or less, and exposure of over 3 months are difficult to interpret since these results do not reflect the timing of reported AEs relative to dosing. Instead these subgroups only reflect the overall incidence of AEs for subjects subdivided into these subgroups on the basis of duration of treatment at the time the data was analyzed for these ongoing OL trials. Common AEs for describing results of OL trials is defined as ≥ 5% incidence in either the ≤ 3 month or > 3 month Total Pal subgroups. This 5% cut-off level was selected by the undersigned reviewer for describing these results, since exposure in the OL was longterm.

Common AEs in the OL trial dataset were generally expected AEs for the study population, the study drug or the drug class while also taking into account the nature of the longterm trial (in which the longer the trial the greater the incidence of a given AE is likely to occur than in the short term trials). The following findings were unexpected to the undersigned reviewer:

- *Tachycardia and/or sinus tachycardia were common unexpected AEs (if they occurred independent of an orthostatic tachycardia). However, tachycardia was reported in Risperdol® approved labeling and is on this basis not an unexpected event. It is difficult to determine if the incidence of tachycardia AEs was dose-dependent for several reasons. Firstly, the event is reported either as sinus tachycardia or tachycardia rather than having these AEs combined. Yet, another problem is distinguishing AEs of tachycardia associated with orthostatic hypotension from tachycardia that is not associated with orthostatic hypotension.*

- *Depression and agitation and anxiety AEs were common but not unexpected for the study population. See section 7.1.4 for "other search strategies" of related AEs. A potential signal for AEs of suicidality may exist at the 15 mg Pal dose-level based on the incidence observed in the pooled short term Phase III trials that employed multiple dose-levels and a placebo control group in a parallel group study design (as previously mentioned).*
- *Nasopharyngitis which was reported more commonly in Pal subjects compared to placebo subjects of the short term Phase III trials was a common AE in the OL longterm trials.*

Some drug-related AEs were reported in <5% of subjects in the pooled OL trial dataset, such as AEs related to extrapyramidal side effects among others.

Completed Phase III Trials -302, -303, -304 and -305.

The following table provides the incidence of AEs as specified (copied from the submission).

Table 8: Treatment-Emergent Adverse Events With at Least 2% Incidence in Any Paliperidone Treatment Group (3 or 6 or 9 or 12 or 15) and Where the Incidence > Placebo by MedDRA Preferred Term - Double-Blind Phase
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

		ER OROS Paliperidone					Olanzapine
Body System or Organ Class Dictionary-derived Term	Placebo (N=355) n (%)	3 mg (N=127) n (%)	6 mg (N=235) n (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)	15 mg (N=113) n (%)	10 mg (N=364) n (%)
Total no. subjects with adverse events	235 (66.2)	91 (71.7)	156 (66.4)	171 (69.5)	184 (76.0)	87 (77.0)	252 (69.2)
Cardiac disorders	43 (12.1)	22 (17.3)	37 (15.7)	45 (18.3)	41 (16.9)	15 (13.3)	52 (14.3)
Atrioventricular block first degree	5 (1.4)	2 (1.6)	0	6 (2.4)	2 (0.8)	5 (4.4)	4 (1.1)
Bundle branch block	6 (1.7)	4 (3.1)	3 (1.3)	7 (2.8)	1 (0.4)	1 (0.9)	9 (2.5)
Sinus arrhythmia	0	3 (2.4)	2 (0.9)	2 (0.8)	1 (0.4)	0	2 (0.5)
Sinus tachycardia	15 (4.2)	11 (8.7)	9 (3.8)	10 (4.1)	17 (7.0)	8 (7.1)	20 (5.5)
Tachycardia	10 (2.8)	3 (2.4)	17 (7.2)	18 (7.3)	18 (7.4)	2 (1.8)	13 (3.6)
Eye disorders	6 (1.7)	3 (2.4)	2 (0.9)	8 (3.3)	8 (3.3)	2 (1.8)	3 (0.8)
Oculogyration	0	0	0	5 (2.0)	0	0	0
Vision blurred	4 (1.1)	1 (0.8)	1 (0.4)	0	5 (2.1)	0	1 (0.3)
Gastrointestinal disorders	58 (16.3)	25 (19.7)	47 (20.0)	44 (17.9)	62 (25.6)	28 (24.8)	62 (17.0)
Abdominal pain upper	2 (0.6)	1 (0.8)	6 (2.6)	5 (2.0)	4 (1.7)	2 (1.8)	2 (0.5)
Diarrhoea	8 (2.3)	1 (0.8)	2 (0.9)	3 (1.2)	6 (2.5)	2 (1.8)	6 (1.6)
Dry mouth	2 (0.6)	3 (2.4)	8 (3.4)	2 (0.8)	7 (2.9)	4 (3.5)	5 (1.4)
Dyspepsia	14 (3.9)	3 (2.4)	6 (2.6)	5 (2.0)	12 (5.0)	6 (5.3)	13 (3.6)
Nausea	19 (5.4)	8 (6.3)	9 (3.8)	10 (4.1)	10 (4.1)	2 (1.8)	8 (2.2)
Salivary hypersecretion	1 (0.3)	0	1 (0.4)	3 (1.2)	10 (4.1)	3 (2.7)	0
Toothache	4 (1.1)	2 (1.6)	5 (2.1)	6 (2.4)	5 (2.1)	2 (1.8)	11 (3.0)
Vomiting	17 (4.8)	2 (1.6)	6 (2.6)	9 (3.7)	12 (5.0)	8 (7.1)	5 (1.4)

General disorders/ administration site conditions	19 (5.4)	7 (5.5)	10 (4.3)	16 (6.5)	17 (7.0)	8 (7.1)	16 (4.4)
Asthenia	3 (0.8)	2 (1.6)	1 (0.4)	5 (2.0)	5 (2.1)	1 (0.9)	2 (0.5)
Fatigue	5 (1.4)	2 (1.6)	2 (0.9)	4 (1.6)	5 (2.1)	0	6 (1.6)
Pyrexia	4 (1.1)	1 (0.8)	1 (0.4)	5 (2.0)	4 (1.7)	1 (0.9)	5 (1.4)
Infections and infestations	28 (7.9)	11 (8.7)	30 (12.8)	21 (8.5)	27 (11.2)	19 (16.8)	24 (6.6)
Nasopharyngitis	10 (2.8)	4 (3.1)	5 (2.1)	4 (1.6)	6 (2.5)	3 (2.7)	5 (1.4)
Upper respiratory tract infection	2 (0.6)	1 (0.8)	2 (0.9)	3 (1.2)	2 (0.8)	4 (3.5)	1 (0.3)
Urinary tract infection	2 (0.6)	1 (0.8)	2 (0.9)	2 (0.8)	0	3 (2.7)	2 (0.5)
Investigations	42 (11.8)	22 (17.3)	31 (13.2)	32 (13.0)	34 (14.0)	18 (15.9)	75 (20.6)
Blood insulin increased	2 (0.6)	3 (2.4)	3 (1.3)	2 (0.8)	1 (0.4)	1 (0.9)	3 (0.8)
Blood pressure increased	2 (0.6)	3 (2.4)	1 (0.4)	1 (0.4)	3 (1.2)	2 (1.8)	1 (0.3)
Blood triglycerides increased	1 (0.3)	2 (1.6)	1 (0.4)	0	0	3 (2.7)	4 (1.1)
Electrocardiogram QT corrected interval prolonged	9 (2.5)	4 (3.1)	9 (3.8)	7 (2.8)	12 (5.0)	4 (3.5)	10 (2.7)
Electrocardiogram T wave abnormal	4 (1.1)	3 (2.4)	2 (0.9)	4 (1.6)	2 (0.8)	2 (1.8)	2 (0.5)
Heart rate increased	2 (0.6)	4 (3.1)	2 (0.9)	1 (0.4)	3 (1.2)	0	2 (0.5)
Weight increased	5 (1.4)	1 (0.8)	0	4 (1.6)	4 (1.7)	3 (2.7)	15 (4.1)
Musculoskeletal and connective tissue disorders	17 (4.8)	5 (3.9)	10 (4.3)	13 (5.3)	21 (8.7)	6 (5.3)	18 (4.9)
Back pain	3 (0.8)	1 (0.8)	2 (0.9)	3 (1.2)	5 (2.1)	0	6 (1.6)
Pain in extremity	4 (1.1)	0	2 (0.9)	0	5 (2.1)	3 (2.7)	2 (0.5)

Table 8: Treatment-Emergent Adverse Events With at Least 2% Incidence in Any Paliperidone Treatment Group (3 or 6 or 9 or 12 or 15) and Where the Incidence > Placebo by MedDRA Preferred Term - Double-Blind Phase
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

		ER OROS Paliperidone					Olanzapine
Body System or Organ Class Dictionary-derived Term	Placebo (N=355) n (%)	3 mg (N=127) n (%)	6 mg (N=235) n (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)	15 mg (N=113) n (%)	10 mg (N=364) n (%)
Nervous system disorders	96 (27.0)	34 (26.8)	68 (28.9)	99 (40.2)	110 (45.5)	47 (41.6)	123 (33.8)
Akathisia	14 (3.9)	5 (3.9)	7 (3.0)	20 (8.1)	23 (9.5)	11 (9.7)	7 (1.9)
Dizziness	14 (3.9)	7 (5.5)	11 (4.7)	11 (4.5)	12 (5.0)	7 (6.2)	19 (5.2)
Dystonia	2 (0.6)	1 (0.8)	3 (1.3)	9 (3.7)	9 (3.7)	1 (0.9)	1 (0.3)
Extrapyramidal disorder	8 (2.3)	6 (4.7)	5 (2.1)	17 (6.9)	18 (7.4)	9 (8.0)	6 (1.6)
Headache	42 (11.8)	14 (11.0)	29 (12.3)	34 (13.8)	35 (14.5)	20 (17.7)	35 (9.6)
Hypertonia	4 (1.1)	3 (2.4)	3 (1.3)	10 (4.1)	8 (3.3)	4 (3.5)	5 (1.4)
Parkinsonism	0	0	1 (0.4)	5 (2.0)	3 (1.2)	2 (1.8)	2 (0.5)
Sedation	13 (3.7)	1 (0.8)	12 (5.1)	8 (3.3)	15 (6.2)	2 (1.8)	24 (6.6)
Somnolence	12 (3.4)	6 (4.7)	8 (3.4)	17 (6.9)	11 (4.5)	7 (6.2)	47 (12.9)
Tremor	12 (3.4)	4 (3.1)	6 (2.6)	11 (4.5)	8 (3.3)	3 (2.7)	8 (2.2)

The following table provides the incidence of common AEs in the elderly Phase III trial (as provided by the sponsor).

Table 27: Incidence of Common[a] Treatment-Emergent Adverse Events (Study R076477-SCH- 302)

Body System or Organ Class Dictionary-derived Term	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)
Total no. subjects with adverse events	27 (71)	51 (67)
Nervous system disorders	9 (24)	22 (29)
Somnolence	2 (5)	7 (9)
Dizziness	0	5 (7)
Extrapyramidal disorder	4 (11)	4 (5)
Headache	1 (3)	4 (5)
Cardiac disorders	5 (13)	20 (26)
Sinus tachycardia	0	7 (9)
Tachycardia	0	5 (7)
Psychiatric disorders	10 (26)	11 (14)
Insomnia	4 (11)	7 (9)
Agitation	2 (5)	2 (3)
Anxiety	2 (5)	2 (3)
Vascular disorders	2 (5)	8 (11)
Hypertension	1 (3)	4 (5)
Hypotension	0	4 (5)
Gastrointestinal disorders	7 (18)	7 (9)
Nausea	2 (5)	2 (3)
Vomiting	2 (5)	1 (1)
Investigations	5 (13)	7 (9)
Electrocardiogram QT corrected interval prolonged	1 (3)	5 (7)
Electrocardiogram T wave inversion	2 (5)	1 (1)
General disorders and administration site conditions	2 (5)	5 (7)
Asthenia	2 (5)	4 (5)

[a] Includes treatment-emergent adverse reported in at least 5% of the subjects in either treatment group.
Cross-reference: Appendix 2.7.4.3.2.1.

The following observation from a table found in the appendix of the SCS for this elderly trial is noted, since a similar potential drug-related signal was observed in the completed Phase III trials of primarily non-elderly subjects. 1° AV block in 3% (2 out of 76 Pal subjects) compared to 0 placebo subjects (out of 38 placebo subjects). This event was not shown in the sponsor in-text summary table in the SCS but rather in Appendix 2.7.4.3.1 of the SCS.

Ongoing Phase III Trial -301.
Since the trial is ongoing and blinded, results were not described.

Ongoing Phase III Open Label Trials -701, -702, -703, -704, and -705.

The following table summarizes the incidence of common (≥5% in any given treatment group) AEs, as provided by the sponsor.

Table 29: Incidence of Common[a] Treatment-Emergent Adverse Events
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
Total no. subjects with adverse events	68 (64)	98 (77)	93 (52)	350 (69)	68 (64)	109 (76)	229 (59)	557 (72)
Nervous system disorders	26 (24)	62 (48)	40 (22)	181 (36)	20 (19)	68 (48)	86 (22)	311 (40)
Akathisia	5 (5)	19 (15)	9 (5)	48 (10)	4 (4)	18 (13)	18 (5)	85 (11)
Headache	4 (4)	11 (9)	11 (6)	54 (11)	8 (8)	20 (14)	23 (6)	85 (11)
Somnolence	4 (4)	9 (7)	4 (2)	32 (6)	2 (2)	17 (12)	10 (3)	58 (7)
Extrapyramidal disorder	6 (6)	13 (10)	6 (3)	24 (5)	3 (3)	9 (6)	15 (4)	46 (6)
Dizziness	1 (1)	7 (5)	4 (2)	21 (4)	4 (4)	6 (4)	9 (2)	34 (4)
Hypertonia	1 (1)	6 (5)	1 (1)	15 (3)	3 (3)	9 (6)	5 (1)	30 (4)
Tremor	4 (4)	5 (4)	3 (2)	15 (3)	0	9 (6)	7 (2)	29 (4)
Dystonia	3 (3)	8 (6)	1 (1)	4 (1)	1 (1)	3 (2)	5 (1)	15 (2)
Psychiatric disorders	24 (22)	41 (32)	39 (22)	160 (32)	33 (31)	60 (42)	96 (25)	261 (34)
Insomnia	9 (8)	18 (14)	16 (9)	53 (10)	12 (11)	20 (14)	37 (9)	91 (12)
Anxiety	5 (5)	7 (5)	9 (5)	37 (7)	10 (9)	10 (7)	24 (6)	54 (7)
Depression	3 (3)	12 (9)	1 (1)	30 (6)	1 (1)	12 (8)	5 (1)	54 (7)
Psychotic disorder	6 (6)	6 (5)	11 (6)	31 (6)	10 (9)	14 (10)	27 (7)	51 (7)
Schizophrenia	2 (2)	4 (3)	6 (3)	31 (6)	8 (8)	8 (6)	16 (4)	43 (6)
Agitation	6 (6)	2 (2)	8 (4)	13 (3)	9 (8)	5 (3)	23 (6)	20 (3)
Infections and infestations	9 (8)	16 (13)	10 (6)	88 (17)	12 (11)	24 (17)	31 (8)	128 (16)
Nasopharyngitis	2 (2)	5 (4)	3 (2)	28 (6)	4 (4)	6 (4)	9 (2)	39 (5)
Cardiac disorders	16 (15)	28 (22)	17 (10)	64 (13)	14 (13)	22 (15)	47 (12)	114 (15)
Tachycardia	2 (2)	8 (6)	7 (4)	25 (5)	3 (3)	9 (6)	12 (3)	42 (5)
Sinus tachycardia	7 (7)	10 (8)	2 (1)	18 (4)	5 (5)	6 (4)	14 (4)	34 (4)
Bundle branch block	5 (5)	3 (2)	2 (1)	7 (1)	5 (5)	2 (1)	12 (3)	12 (2)

Note: Percentages calculated with the number of subjects in each group as denominator.
[a]Adverse events occurring in ≥5% of subjects in any treatment group.

See recommendations in the final section of this review regarding the above AEs.

"Significant" AEs were previously described in a subsection on "Other Significant" AEs (Section 7.1.3.3) and results of a search for specific AE terms in either the study report or in subject narratives were previously described in Section 7.1.4.

7.1.5.1 Eliciting adverse events data in the development program

The above sections are in reference to spontaneous reported AEs, as is standard procedure. Any special rating scales that might be considered as elicited AEs are also described, elsewhere, in the appropriate subsection of this review.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Categorization and preferred terminology is based on the MedRA system. Several categorization and preferred term systems exist of which MedRA is one (e.g. WHO system is another).

Reviewer Comments. *Each AE categorization system has its inherent limitations. The MedRA system is now considered the preferred categorization system by the Agency at this time, to the knowledge of the undersigned reviewer.*

7.1.5.3 Incidence of common adverse events

See Section 7.1.5

7.1.5.4 Common adverse event tables

See Section 7.1.5

7.1.5.5 Identifying common and drug-related adverse events

See Section 7.1.5

7.1.5.6 Additional analyses and explorations

See Section 7.4.2 of this review for additional analyses of AEs by demographic features, for drug-drug interactions and other analyses.

7.1.6 Less Common Adverse Events

The focus of this review is on common AEs, AEs of special interest, SAEs and ADOs as described in previous sections which include less common AEs.

7.1.7 Laboratory Findings

A Caveat on Group and Time-point Comparisons on a Given Clinical Parameter. *Results of statistical group or time-point comparisons or in-text description of statistical results on clinical parameters could not be found in the SCS. Therefore, group and time-point comparisons described in this review on any given clinical parameter are based on numerical comparisons,*

unless otherwise specified (results on clinical parameters that were found in the SCS and are described in this review did not include statistical comparisons).

7.1.7.1 Overview of laboratory testing in the development program

See study schedules in Table series 10.1 in the appendix of this review.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See sections below and Section 7.1 for a description of datasets analyzed and described in this review.

7.1.7.3 Standard analyses and explorations of laboratory data

See below.

7.1.7.3.1 Analyses focused on measures of central tendency

See Table Series 10.1 for schedule of assessments in Phase III trials.

Routine laboratory and urinalysis assessments were planned at the following time-points for the completed short-term non-elderly and elderly Phase III trials:

- At screening
- Baseline and on
- Days 15, 43 with DB treatment given on Days 1-42.
- Study Endpoint scheduled for 7 days after the last day of DB treatment (on Day 50 or upon early withdrawal)

Routine laboratory and urinalysis assessments were planned at the following time-points for the OL Extension Trials:

- Baseline of the OL Extension Trial
- Weeks 12, 24, 52 with OL Pal treatment planned for one year (weeks 1-52) for Studies -703 through -705 and for 6 months in Study -702.
- Study Endpoint

Results on each clinical parameter showing mean changes from baseline to each assessment time-point were found in appendices of the SCS (the SCS provided mean change from baseline to endpoint for selected parameters).

Reviewer Comments and Caveats on Overall Potential Limitations Found Upon Review of Results that were Found in the SCS

Results of statistical group and/or time-point comparisons could not be found in the sponsor's summary tables that were found in the SCS or in the more complete tables found in the appendix (as shown later in this review). Therefore, reviewer comments on group or time-point differences are based on numerical comparisons.

Descriptive statistical results on several urinalysis parameters either could not be found or were only found for a small subgroup of subjects (could not be found in the SCS or in appendices) or in some cases urinalysis results appeared to reflect contaminated specimens (i.e. a number of RBCs were found in urine samples in most treatment groups in one of the Phase I/IIa datasets as described later). Fortunately, these problems did not exist for all datasets such that some useful information could be gleaned from some of the datasets to sufficiently assess safety. While urine ketone results would be helpful given that hyperglycemia is reported to occur with drugs in this drug-class, other safety information could be used to assess safety regarding potential effects on glucose regulation (e.g. glucose plasma levels, results of SAEs, ADOs and other safety data).

Most laboratory parameters had large standard deviations. CPK levels were most remarkably variable which is not unexpected given the study population in the Phase III trials. Since the variance on CPK was large, it is also not surprising that some treatment groups showed remarkable mean changes (increased or decreased) that were generally inconsistent. However, results of Phase I trials on this parameter could be examined.

Another problem with laboratory results found in the SCS is that for at least some of the safety datasets values could only be found for a subgroup of subjects (e.g. on 76 out of 138 subjects LD OROS Pal treated subjects had CPK results found in a summary table on the incidence of CPK outliers found on page 3637 in an appendix of the SCS).

The in-text tables of the SCS only showed results of selected parameters and showed sample sizes, mean baseline ±SD, mean change from baseline to endpoint±SD, but the range of values for selected datasets could not be found (the completed short-term Phase III trials and the ongoing OL Extension Trials as described below). However, these results could generally be found in appendices, unless otherwise specified in this review (e.g. incidence of outliers on some parameters could not be found and were later provided by the sponsor upon request). A description of Phase I/II results could generally not be found in the SCS but results could be found in tables provided in appendices of the SCS, as specified below.

Comments on Potential Limitations with the OL safety dataset

The OL safety dataset was limited by the number of subjects exposed to over 6 months of treatment, since these trials are ongoing. The majority of longterm safety data beyond 6 months was provided later in a 120-Day SUR which is covered in Section 7.2.9 of this review. Sample sizes at given time-point were further limited for several treatment subgroups in the N000 submission since subjects were not only subgrouped by their previous DB treatment assignment (placebo, Pal or olanzapine in the lead-in studies) but also by the duration of treatment (≤ 3 month and > 3 month exposure subgroups). Fortunately results of subjects from all treatment subgroups, combined ("Total" Pal group) were provided for these 2 exposure subgroups. The

results of the largest exposure subgroup (the > 3month Total Pal group) was the focus of review for the 24 week assessment time-point since this subgroup had 462 subjects at this time-point (the ≤ Total Pal subgroup had 131 or fewer subjects assessed at this time-point and at later time-points, and only 7 subjects were found to be assessed at week 52 for the largest subgroup). Consequently, the results of other subgroups and other time-points in the N000 submission are generally considered to be seriously limited. The sponsor used 5/31/05 as their cut-off date for their safety data analyses. See Section 7.2.9 of this review for updated OL results in which the number of subjects exposed to 12 months of Pal had met ICH guidelines and the number exposed to at least 6 months of treatment was larger for any given treatment subgroup.

Short-Term Phase III Safety Datasets (Trials -303, -304 and -305, combined and the elderly Trial -302).

Reviewer Comment. *Key findings are outlined below and are followed by data from the sponsor's summary tables:*

- *Inconsistent but remarkable CK results: Although mean increases in CK were observed among treatment groups in the 2 safety datasets, the observations were inconsistent. Given the following observations results on CK are difficult to interpret due to fluctuating levels over time during placebo treatment and elevations observed at baseline:*
  - *Treatment group mean increases in CK were inconsistent across dose-levels of Pal, and when compared to mean changes in the placebo group.*
  - *Results were also inconsistent across the 2 safety datasets.*
  - *Mean CK values at baseline were somewhat elevated in several treatment groups.*
  - *The within group variance (the SD) for a given treatment group was large (approximately 125 to over 400 U/l).*
  - *The placebo group also showed inconsistent mean increases in CPK over some time-points and high group mean values on some time-points (e.g. 573 U/l group mean value at Day 43), as revealed by a review of mean change of CPK over time (from baseline to each time-point of assessment) that was found in Appendix 2.7.4.4.11 of the SCS (data not shown below).*
  - *Finally, large fluctuations in CPK were also observed over time in some individual placebo subjects (e.g. from 172 U/l to 1208 U/l), as found in Appendix 2.7.4.4.2.1 for the 3 Phase III trial dataset.*
  - *Therefore, results on CPK are difficult to interpret.*
  - *While the above findings appear to reflect underlying elevations of CPK that are reported to occur with the schizophrenia-acute population, results from Phase I trials also show some elevations as described later that suggest the need for further explanation or exploration.*
- *Reproduceable Mean Decreases in Hemoglobin in Pal Groups with a Magnitude of Change that is Considered Clinically Unremarkable:*
  - *Group mean decreases in hemoglobin were observed Pal treatment groups that were not observed in placebo groups in both the non-elderly and elderly trial datasets, respectively (see data below).*

- *The magnitude of these mean changes was clinically unremarkable (a group mean change of up to 4.3±8.4, SD, in units of g/l was observed among the pal groups in the 2 safety datasets).*
- *Also mean changes generally did not show a trend for a greater mean change with increasing dose-levels.*

- *Reproduceable Pal Group Mean Decreases in Platelet Count of a Clinically Unremarkable Magnitude of Change:*
  - *Pal group mean decreases in platelet count of up to -15.6±58.5 (SD) units (units are in giga/l) were observed in both safety datasets (the pooled non-elderly trials and the single elderly trial, respectively).*
  - *The placebo groups in each safety dataset showed little change or a mean increase in this parameter (a mean increase of up to 22.6±57.8 units). However, the magnitude of the mean decrease in platelet count in each Pal group is not clinically remarkable.*

Other laboratory parameter results on mean change from baseline on a given parameter were clinically unremarkable and failed to reveal any unexpected drug effect.

The following are key results copied from sections of summary tables provided in the SCS:

Table 69: Selected Clinical Laboratory Analytes: Change From Baseline to End Point
(Pooled Double-Blind Studies R076477-303, 304, 305: Safety Analysis Set)

	Placebo (N=355)	ER OROS PAL 3 mg (N=127)	ER OROS PAL 6 mg (N=335)	ER OROS PAL 9 mg (N=246)	ER OROS PAL 12 mg (N=243)	ER OROS PAL 15 mg (N=113)	Total Paliperidone (N=963)	Olanzapine 10 mg (N=364)
Creatine kinase (U/L)								
N	329	130	315	235	230	110	910	353
Mean baseline (SD)	149.8 (179.72)	160.6 (220.83)	171.7 (555.95)	151.1 (229.82)	173.4 (529.61)	134.3 (149.40)	160.6 (484.81)	186.9 (386.42)
Mean change (SD)	30.7 (455.40)	-6.9 (237.66)	25.5 (617.14)	-9.1 (253.62)	-6.6 (521.95)	5.4 (100.22)	1.7 (427.83)	-18.1 (449.75)
Platelets (giga/l)								
N	325	119	313	227	225	108	892	341
Mean baseline (SD)	272.6 (72.51)	297.5 (79.18)	285.4 (77.59)	283.5 (84.91)	281.2 (73.65)	301.2 (82.67)	287.4 (78.54)	279.1 (76.57)
Mean change (SD)	6.0 (54.04)	-13.6 (57.59)	-6.6 (55.11)	-7.5 (55.61)	-11.2 (47.41)	-15.6 (58.50)	-10.0 (54.16)	-1.4 (51.89)
Reticulocytes (%)								
N	319	118	306	221	219	109	873	335
Mean baseline (SD)	1.8 (0.76)	1.7 (0.88)	2.0 (0.77)	1.9 (0.82)	1.9 (0.70)	1.9 (1.24)	1.9 (0.86)	1.0 (1.07)
Mean change (SD)	-0.0 (0.55)	-0.1 (0.69)	-0.1 (0.47)	0.0 (1.76)	-0.1 (0.53)	-0.1 (1.08)	-0.1 (1.05)	0.1 (1.62)
Hemoglobin (g/L)								
N	328	120	314	228	227	110	899	344
Mean baseline (SD)	146.5 (16.28)	145.9 (13.87)	145.6 (16.12)	144.6 (15.63)	144.6 (16.04)	143.5 (15.18)	144.9 (15.56)	147.6 (15.19)
Mean change (SD)	-0.1 (9.72)	-2.2 (8.51)	-4.3 (8.42)	-4.0 (8.49)	-3.0 (8.80)	-3.0 (7.71)	-3.5 (8.48)	-3.0 (9.20)

Table 70: Selected Clinical Laboratory Analytes: Change From Baseline to End Point
(Study R076477-302: Safety Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)
Creatine kinase (U/L)		
N	36	75
Mean baseline (SD)	119.9 (194.15)	75.7 (38.03)
Mean change (SD)	-3.9 (217.71)	34.4 (113.12)

Hemoglobin (g/L)		
N	37	74
Mean baseline (SD)	133.6 (13.33)	132.1 (13.71)
Mean change (SD)	1.3 (7.90)	-3.6 (9.05)
Platelets (giga/l)		
N	37	73
Mean baseline (SD)	247.4 (81.03)	259.7 (86.83)
Mean change (SD)	22.6 (57.77)	-8.0 (52.52)

Ongoing Phase III Trial -301.
Results not provided. The study is blinded and ongoing.

Ongoing Phase III Open Label Trials -703, -704, and -705.
Reviewer Comment. *Upon review of the >3month and ≥ 3 month "Total Pal" subgroups of the OL extension trials (see table below for each treatment subgroup analyzed by the sponsor), the results were generally found to be similar to previously described results of the two short-term, completed Phase III trial datasets. The following outlines key observations are noted (based on numerical comparisons of the sponsor's results, as provided in the submission):*

- *CK Mean Increase (from baseline to study endpoint) in the ≤ 3 month total Pal group:*
  - *The ≤3 month Pal group showed a mean increase in CK with little to no mean change in the > 3 month Pal group.*
  - *However, these results are difficult to interpret in the absence of a placebo group.*
  - *Furthermore, mean values at baseline were elevated in some subgroups and standard deviations for each subgroup were large.*
  - *Consequently, results are difficult to interpret.*
- *Group mean decreases in platelet count (from baseline to study endpoint in the >3 month and the ≤ 3 month subgroups) were observed (based on results found in-text summary tables in the SCS that are clinically unremarkable in magnitude were observed.*
  - *The >3 month subgroups generally showed numerically greater mean decreases than the ≤3 month subgroups, suggesting that a potential drug induced decrease in platelet count increases with duration of treatment.*
  - *Without a placebo group, these results are difficult to interpret and the magnitude of the observed decreases is clinically unremarkable for the duration of treatment examined.*

The following results were copied out of the sponsor's in-text summary table.

Table 71: Selected Clinical Laboratory Analytes: Change From Baseline to End Point
(Pooled Open-Label Studies R076477-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=3 months (N=107)	Pla/Pali >3 months (N=128)	Pali/Pali <=3 months (N=178)	Pali/Pali >3 months (N=505)	Olan/Pali <=3 months (N=106)	Olan/Pali >3 months (N=143)	Total Pali <=3 months (N=391)	Total Pali >3 months (N=776)
Chemistry (continued)								
Creatine kinase (U/L)								
N	43	93	63	324	42	94	147	511
Mean baseline (SD)	179.3 (237.60)	115.5 (117.43)	148.0 (197.71)	144.8 (455.06)	160.3 (153.07)	152.2 (332.78)	150.7 (198.30)	140.8 (390.88)
Mean change (SD)	6.1 (215.26)	34.7 (118.26)	91.5 (182.83)	-10.2 (454.02)	32.4 (406.78)	1.9 (358.73)	63.9 (274.17)	0.2 (396.02)

Hemoglobin (g/L)								
N	42	91	59	306	41	89	142	486
Mean baseline (SD)	144.9 (14.19)	143.0 (15.38)	144.9 (13.89)	143.2 (15.37)	146.1 (14.60)	146.7 (13.03)	145.2 (16.32)	143.8 (15.01)
Mean change (SD)	-2.9 (9.29)	-2.7 (9.96)	-3.5 (10.88)	-2.1 (10.34)	-2.9 (8.99)	-3.1 (9.94)	-2.7 (9.84)	-2.3 (10.18)
Platelets (giga/l)								
N	42	89	59	303	40	87	141	479
Mean baseline (SD)	264.1 (74.45)	260.0 (76.16)	281.4 (77.33)	276.2 (77.54)	271.5 (65.48)	293.6 (79.70)	273.4 (73.13)	276.4 (78.19)
Mean change (SD)	-9.6 (47.11)	-2.2 (54.80)	-0.6 (44.81)	-15.4 (62.85)	-6.4 (38.86)	-26.7 (61.63)	-4.9 (43.79)	-15.0 (61.54)

Since the sponsor's in-text summary table on showed mean changes from baseline to endpoint (after treatment cessation), on-treatment data that was found in Appendix 2.7.4.4.1.2 of the SCS was reviewed. The table in this appendix was too long to show in this review but it should descriptive statistical results for each assessment time-point. Upon review of this table, the following additional observations were made by the undersigned reviewer.

1. Additional Observations on Decreases in Group Mean Platelet count upon review of results that include on-treatment time-points

- *At 6 Months of Treatment Mean and median Decreases in Platelet Count of approximately -15 to -17 giga/l, respectively were observed (insufficient data after 6 months) in the Total Pal group:*
  - *The > 3 month Total Pal group showed mean and median decreases of approximately -15 to -17giga/l after 6 months of treatment (at week 24 with insufficient data after 6 months). This subgroup was large, consisting of at least 450 subjects for 6 month and previous time-points which includes all subjects in the OL ongoing trials, as of the 5/31/05 cut-off date).*
- *At 6 months of treatment approximately -25 to -30 giga/l in the > 3 month subgroup that previously received DB Olanzapine treatment in the 6-week Short term Lead-in Trials was observed (upon review of On-Treatment Data found in Appendix 2.7.4.4.1.2 of the SCS):*
  - *The > 3 month DB Olanzapine/OL Pal subgroup (received DB olanzapine in the lead-in study) showed a mean or median decrease of up to -25 or -30 giga/l at the 6 months (week 24) and at study endpoint for the >3 month subgroup that previously received DB olanzapine treatment (DB Olanzapine/OL Pal subgroup). The sample size for this subgroup was 87 for these time-points.*
  - *The above results are compared to those of the DB Pal/OL Pal subgroup (received Pal treatment during the DB treatment phase of the lead-in study followed by OL Pal) showed a mean and median decrease of -17 giga/l at 6 months in which the sample size was over 280 subjects for this time-point. The sample sizes were insufficient for other OL on-treatment time-points which were the 12 week and 52 week time-points of this subgroup and for the ≤ 3 month subgroup of this DB Pal/OL Pal subgroup.*
  - *Other subgroups generally had insufficient sample sizes at any given on-treatment timepoint during OL treatment.*
  - *The following additional findings are noted as well as a more detailed description of results in the olanzapine/pal subgroup showing the largest numerical mean and median decreases. Mean or median decreases for any given time-point were generally less than -10 giga/l for any given treatment group except for the >3 month subgroup that previously received olanzapine treatment during the DB treatment phase of the lead in studies that preceded the OL extension trials. This*

subgroup showed a mean and median decrease of approximately -25 to -30 giga/l at weeks 24 (n=87) and study endpoint (n=87, which occurred days after treatment). The only post-6 month OL treatment phase assessment time-point in the dataset was at week 52. Only 1 subject had data at week 52 in this subgroup who did not show a decrease in platelet count (and only 7 total subjects with data for all subgroups, combined). These observations can only be considered preliminary due to serious limitations with this dataset, as previously discussed.

- *Since the standard deviations were generally large (e.g. approximately ±78 giga/l was observed in a given subgroup at any given time-point) the above observations would not reach statistical significance upon pairwise comparisons between treatment groups or between time-points in a given treatment group.*
- *The minimum within treatment group value for this parameter was approximately 61 giga/l among all the subgroups and among all time-points, but this value or a low within group value of approximately 90 were only observed for a few data points. Most values for any given time-point and any given subgroup were over 100 giga/l. Furthermore, low minimum within group values (as low as approximately 61) were also found on a few baseline or screening time-points (prior to treatment and before the DB phase). Therefore, these low minimum values were not consistent on or off treatment and do not alone provide evidence for a remarkable drug effect on hemoglobin levels.*
- *On-treatment Mean and Median Platelet Decreases Appear to be Greatest in Magnitude after Long term treatment (based on 6 month data, as described in the previous bulleted item) compared to Short-Term DB treatment Time-points (based on results in Appendix 2.7.4.4.1.2 of the SCS).*
  - *Mean and median decreases in the OL Pal subjects during the DB treatment phase were generally between approximately -1 to -10 giga/l per OL treatment subgroup, compared to the larger median and mean decreases observed in the described under the previous bulleted items describing OL Pal results.*
  - *It is also important to note that this pattern of smaller decreases during DB treatment compared to decreases observed with OL longer term treatment was observed for all treatment subgroups over almost all time-points during these DB and OL treatment phases.*
  - *The DB placebo/OL Pal subgroup which had the shortest total duration of Pal exposure over the lead-in and extension trials had an insufficient sample size during OL treatment time-points which still showed a trend for drug-induced decrease in platelet count (mean and median changes during placebo treatment were approximately 7 to 11 giga/l for any given time point compared to a mean decrease of -11 giga/l and a median decrease of -5 giga/l at 6 months.*
  - *These results are only considered preliminary given the serious limitations with this dataset, as previously discussed. See the final section of this review for more comments and recommendations.*

2. *Group mean decreases were observed at on-treatment time-points for hemoglobin that is clinically unremarkable in the observed magnitude of change. These observations were found upon review of data shown below (upon review of Appendix 2.7.4.4.1 for the mean change from baseline to 24 week time-point) as follow:*

- *The 6 month time-point showed a mean and median change of up to -3 or -4 g/l but generally -2 g/l or less in any given treatment subgroup either during the preceding DB treatment phase of lead in studies or during OL treatment up to 6 months (inadequate data past the 6 month time-point (results of he lead in studies that preceded OL extension trials were are also provided in Appendix 2.7.4.4.1).*
- *The standard deviation for each data point was generally at approximately ±15 g/l, such that the above observations would not be statistically significant upon pairwise group or time-point comparisons.*
- *The minimum within group values of hemoglobin approximately 80 or above observed on several time-points of several subgroups, but were not consistently low over time within a given subgroup and were also observed in several subgroups at baseline or screening.*

No other clinically remarkable mean changes were observed in the 2 Total Pal ≤ 3 month and > 3 month exposure subgroups.

Phase I/IIa Studies.

17 Healthy Subject Phase I Studies.

Reviewer Comment. *Results described in this subsection are based on a review of results on the mean change from baseline to treatment endpoint (LOCF data) in the 17 Phase I dataset (healthy subject Phase I pooled results were found in Appendix 2.7.4.4.3.1 of the SCS). Treatment conditions in this pooled dataset included the following (results based on numerical comparisons between treatment conditions are described below): placebo, Low Dose OROS Pal (LD OROS Pal group), High Dose OROS Pal (HD OROS Pal group), IR Pal, and "Other" Pal groups. Refer to Section 7.1 of this review for details on the treatment conditions employed in these studies and refer to Section 4.2 of this review for the overall study design of each study in this pooled dataset.*

Before describing the results of this pooled, Phase I, safety-dataset, it is important to note that results are generally difficult to interpret for a number of reasons. Most Phase I trials were SD, OL, cross-over studies that did not include a placebo group. Only 20 total subjects received placebo in this pooled dataset. Other treatment groups were also small, while between subject variance on most parameters was large. Given the large variance (large SDs) for each treatment condition numerical pairwise comparisons between treatment conditions would not generally reach statistical significance (e.g. differences were generally not greater than 2 SDs of the group mean).

See a previous discussion of other potential limitations in the dataset and on urinalysis results.

In some cases, data could not be found as follows. Data could not be found on a few laboratory parameters in the sponsor's tables (in the above mentioned appendix) for one or a few treatment conditions (e.g. results on CPK for placebo and a few active treatment conditions, as described later). The sponsor was asked about CPK results and a response was provided that is under review (the N005 submission was obtained late in the review cycle).

Given the potential limitations in interpreting pooled Phase I results minimal to no mean changes were observed in each treatment group on most laboratory parameters or results were clinically unremarkable or inconsistent. The following are key observations of unexpected findings, while noting that these results are generally difficult to interpret for reasons already provided and are considered preliminary observations:

- *Mean Increase in CPK that is Greatest in the High-Dose OROS Pal Treatment Condition. The greatest mean increase in CPK were observed in the HD Pal OROS treatment condition (46.9±542.3 U/l) with little to no mean increases in the LD Pal OROS treatment conditions (3.3±189 U/l) and in the IR Pal treatment condition (9.0±97 U/l). Mean baseline CPK values for each treatment condition were within approximately 98 and 116 U/l.*
  - *Results of placebo subjects, the "Other" Pal and the risperidone treatment conditions could not be found in the sponsor's table in the above appendix of the SCS. It is difficult to interpret these results due to the large between subject variance (large SDs) and in the absence of data from a placebo treatment condition (the sponsor was asked about placebo results and a N005 response was recently received late in the review cycle).*
  - *Given the large standard deviations, observed numerical differences between treatment conditions would not generally be statistically significant upon pairwise comparisons (the differences were generally not greater than 2 SDs of the treatment condition means). The results suggest a possible mean increase in CPK with high dose OROS Pal in contrast to low dose OROS Pal and non-OROR or IR formulations.*
  - *Despite the difficulties in interpreting the above results, the findings appear to be reproduceable since similar group mean increases were observed in the HD OROS Pal group in the schizophrenia,-Phase I trial dataset as described later in a subsection below.*
- *Inconsistent Mean Changes in Platelets with a Magnitude of Change that is Clinically Unremarkable. While placebo subjects showed a mean change of -7.9 in platelet count (all values are in units of giga/l), the IR Pal and "other"Pal (non-OROS) Pal groups showed a mean change of approximately 12. However, the standard deviations were large (approximately ±30), such that group differences would not be statistically significant upon pair-wise comparisons (e.g. group differences were generally not greater than 2 standard deviations from the group mean). Furthermore, both OROS groups (LD and HD groups) failed to show a mean increase in platelet count (-6.8 and -1.7, respectively, with SDs of approximately 30). Due to the large SDs it is also difficult to interpret these results. Furthermore, the magnitude of group mean changes is clinically remarkable for all groups examined.*

Schizophrenia Phase I/IIa Trials.

Reviewer Comments. *The following summarize key findings on mean change from baseline to treatment endpoint (LOCF) for laboratory parameters in treatment groups of the schizophrenia Phase I trial dataset (based on a review of Appendix 2.7.4.4.3.1 of the SCS that provided these*

results in which numerical group comparisons were made by the undersigned reviewer, as with previously described results in this review).

The results described in this section are generally difficult to interpret due to major limitations with the dataset or study design of the Phase I trials, as described in the following. The Phase I/IIa Schizophrenia trials were generally OL, MD, non-placebo controlled trials. The exception was a MD DB study but only one group of subjects received a placebo treatment condition that was only given on Day 1 followed by Pal on subsequent treatment days in this MD trial. Sample sizes were generally small (e.g. only approximately 30 Pal IR subjects) while between subject variance was often large for a given parameter for a given treatment condition.

While, results were generally found for the IR Pal and HD OROS Pal treatment conditions (as well as a Risperidone condition) results on a few parameters for 1 or 2 of these treatment conditions could not be found in the above mentioned appendix (e.g. mean CPK values for the Pal IR treatment condition).

While considering the serious limitations with the dataset, the results generally failed to show evidence for a clinically remarkable drug effect (often little to no mean changes were observed on each parameter or observed mean changes were clinically unremarkable or mean changes were inconsistent across treatment conditions). The following key findings are possible exceptions to this overall conclusion:

- *Mean Increase in CPK in the High-Dose OROS Pal Treatment Condition and in the Risperidone Treatment Condition . Similar to that observed in the Phase I dataset of healthy subjects, the schizophrenia-Phase I trial dataset also showed mean numerical increases in CPK in the HD OROS Pal condition of 105 U/l. A LD OROS Pal group was not included in these pooled schizophrenia trial. Results of the risperidone treatment condition were found that showed a small mean increase of 26 U/l. However, the within group variance (standard deviation) was large such that these results are difficult to interpret (SD of 798 for the HD OROS Pal condition). Results of the Pal IR treatment condition could not be found for this parameter in Appendix 2.7.4.3.2*
- *Platelet count mean changes were generally small increases that were clinically unremarkable and difficult to interpret (given the large SDs and other factors). The observed mean changes were 6.7, 11.1 and 16.9 giga/l for the IR Pal, HD OROS Pal and Risperidone treatment conditions, respectively while the standard deviation was approximately 40 in each treatment condition (in units of giga/l).*

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Only the incidence of outliers was described in the SCS and in-text summary tables only showed results of selected parameters and could not find results anywhere in the SCS for all Phase III safety datasets (e.g. could not be found in other sections of the SCS or in an appendix to the SCS). However, this information was provided upon request and reviewed. No new or clinically remarkable findings were revealed upon review of parameters that were omitted from the in-text summary tables found in the SCS.

See the next subsection below on marked outliers regarding subjects identified as being remarkable outliers on LFT based on information provided by the sponsor upon request.

Reveiwer comment. *The following describes results on the 3 safety datasets of Phase III trials. The 2 safety datasets for the completed, short-term Phase III trials are described (the pooled non-elderly trial dataset of Studies -303 through -305 and the elderly trial dataset, Study -302), as well as the results of the OL extension trial dataset (pooled data from OL Studies -702 through -705). The observations noted here, are based on a examination of the incidence of outliers as provided in summary tables in the SCS, as provided by the sponsor (with group numerical comparisons of treatment groups).*

Data supporting key observations noted in the following paragraphs are provided in tables that follow the description of the results.

The incidence of outliers on any given parameter in the three Phase III trial datasets were generally 0-1 % with a few exceptions, as follows. A few parameters showed an incidence of 2% or greater but these parameters failed to show clinically remarkable groups differences between each Pal group and the placebo group (e.g. up to 6-13% incidence of outliers on low HDL values across treatment groups of which 10% of placebo subjects were outliers on this parameter). The few exceptions to this general observation are noted below with additional comments of relevant negative findings for a given signal (e.g. regarding CK outliers).

The following are potential key comments regarding results of the two completed Phase III trial datasets (also see actual results following this italicized section):

- *A Potential Signal for a Greater Incidence of High LDL Outliers in Pal Groups compared to Placebo. The incidence of outliers for high LDL values was greater in Pal groups compared to placebo in the pooled short-term Phase III trial dataset, while Pal and placebo groups were similar on the incidence of outliers of low LDL values.*
- *The Potential Signal on High LDL Outliers was not Observed in the Elderly Trial. A Pal related signal for outliers on high LDL values that was observed in the non-elderly Phase III trial dataset (as above) was not observed in the elderly Phase III trial. However, this elderly trial was optimally designed for detecting a potential signal on potential group differences for a given parameter. The sample size of the treatment groups in this study were small and only one Pal group at a flexible dose design was examined, rather than employing multiple dose levels in a parallel group design. Furthermore, the detection of a signal may be more difficult in this older age-group, since LDL values are commonly elevated in elderly subjects and more likely to be further elevated in elderly patients with schizophrenia (consider for example a potential ceiling effect, as well as greater between individual variance on values). Consequently, it is difficult to make conclusions on the basis of the results of this study, alone and the results are only considered as preliminary.*
- *The Results on CK Outliers is Unremarkable. Results on the incidence of CK outliers by treatment group were unremarkable.*

- *Inconsistent and Clinically Unremarkable Observations on Low Reticulocyte Count Outliers. The incidence of outliers on low reticulocyte counts in any given group was higher than 1% (ranging form 2 to 8% in any given group).*
  - *However, the incidence in any given Pal group in the non-elderly Phase III trial dataset was not remarkably greater to the incidence observed in placebo groups.*
  - *Results across dose-levels of Pal in the pooled dataset failed to show consistent dose-dependent differences on the incidence of these outliers.*
  - *In the elderly trial 8% of Pal subjects were outliers (on low reticulocyte count) compared to 3% of placebo. It is not clear if this a drug-related signal or a false positive finding (e.g. due to multiple comparisons on multiple parameters).*

The following are key observations in the pooled OL trial dataset. The incidence of 0-1% in the ≤ 3month and > 3 month total Pal groups except for the incidence of outliers on:

- *The Pal subgroups showed an incidence of 4 or 7 % for high LDL outliers (for ≤3 month and > 3 month groups, respectively) and of 16 and 11%, respectively, for low LDL outliers. While the clinical significance of these findings is difficult to interpret it is notable that no subjects were outliers on high HDL but all groups except for one of them had an incidence within 7 to 9% in any given group for low HDL. This finding may have clinical relevance but without a placebo group this finding is only considered preliminary.*
- *The incidence of low reticulocyte count in contrast to that of high reticulocyte count suggests a possible drug-related signal for low reticulocyte count. Yet this observation is not consistent across groups and can only be considered preliminary since a placebo group is not included. Furthermore, the finding alone is not considered clinically remarkable.*

No Outliers on Low Platelet Count or on Low values of Red Cell-related Parameters. Given previous observations for reproduceable mean decreases in platelet counts and hemoglobin in placebo controlled Phase III trial datasets, no Pal subject in any Phase III trial met outlier criteria for low platelet count, low hemoglobin, low red blood cell count or low hematocrit (in the non-elderly Studies -303 through -305, elderly trial -302 and OL extension trials -702 through -705).

Laboratory results from the ongoing, blinded "prevention of recurrence" Phase III trial (Study -301) and it's corresponding OL Extension Study -701 were not provided by the sponsor (since the trial is ongoing and blinded at this time).

The following tables were copied from sections of summary tables found in the SCS (see above review comments).

Table 72: Treatment-Emergent Markedly Abnormal Laboratory Results
(Pooled Double-Blind Studies R076477-303, 304, 305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=346) n (%)	ER OROS PAL 12 mg (N=342) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
LDL (mmol/L)	328	118	212	234	229	109	902	345
Abnormally high	20 (6)	14 (12)	29 (14)	14 (6)	19 (8)	4 (4)	80 (9)	45 (13)
Abnormally low	43 (13)	19 (16)	28 (13)	42 (18)	30 (13)	20 (18)	139 (15)	24 (7)
Creatine kinase (U/L)	330	121	215	236	231	110	913	353
Abnormally high	6 (2)	0	4 (2)	1 (<1)	4 (2)	1 (1)	10 (1)	10 (3)
Abnormally low	0	0	0	0	0	0	0	0
Reticulocytes (%)	321	120	207	223	219	109	878	339
Abnormally high	3 (1)	0	1 (<1)	3 (1)	2 (1)	1 (1)	7 (1)	9 (3)
Abnormally low	11 (3)	9 (8)	7 (3)	8 (4)	4 (2)	5 (5)	33 (4)	7 (2)

It is noteworthy that none of the subjects in Study -302 met outlier criteria for high CPK, despite the previously shown markedly greater group mean elevation in CPK from baseline during treatment in Pal subjects that was not observed in the placebo group.

Table 73: Treatment-Emergent Markedly Abnormal Laboratory Results
(Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=75) n (%)
LDL (mmol/L)	37	73
Abnormally high	1 (3)	0
Abnormally low	5 (14)	9 (12)
HDL (mmol/L)	37	75
Abnormally high	0	0
Abnormally low	1 (3)	3 (4)
Reticulocytes (%)	37	74
Abnormally high	1 (3)	2 (3)
Abnormally low	1 (3)	6 (8)

Table 74: Treatment-Emergent Markedly Abnormal Laboratory Results
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) N (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
LDL (mmol/L)	39	91	60	313	43	92	142	496
Abnormally high	2 (5)	5 (5)	4 (7)	13 (4)	4 (9)	3 (3)	10 (7)	21 (4)
Abnormally low	6 (15)	11 (12)	8 (13)	31 (10)	9 (21)	14 (15)	23 (16)	56 (11)
HDL (mmol/L)	42	93	63	321	43	93	148	507
Abnormally high	0	0	0	0	0	0	0	0
Abnormally low	1 (2)	8 (9)	5 (8)	28 (9)	4 (9)	7 (8)	10 (7)	43 (8)
Reticulocytes (%)	41	88	59	304	42	87	142	479
Abnormally high	0	0	0	5 (2)	0	1 (1)	0	6 (1)
Abnormally low	3 (7)	7 (8)	1 (2)	12 (4)	0	1 (1)	4 (3)	20 (4)

The sponsor did not describe any observations from individual subject outliers.

Phase I/IIa Studies.
The incidence of outliers was found in Appendix 2.7.4.4.3.4 and results are described based on numerical observations or numerical comparisons between treatment conditions. Refer to the previous section of this review (7.1.7.3.1) for a discussion of serious limitations with interpreting results of the Phase I/II safety datasets described in the SCS that are also described in this review.

17 Healthy Subject Phase I/IIa Studies.
Reviewer Comment. *See previous discussions on the serious limitations with interpreting laboratory results in Phase I/II Trials. The incidence of outliers were generally 0 to 1% in any given treatment condition on any given parameter with a few exceptions. The few exceptions were as follows:*

- *High CPK outliers among Subjects treated with OROS Pal but not in Placebo and non-OROS Pal Treatment Conditions.*
  - *No subjects had high outlier values for CPK in the placebo, IR Pal, "other' Pal or risperidone treatment conditions.*
  - *In contrast to these groups the incidence of high CPK outliers in the LD OROS Pal, HD OROS Pal and all OROS Pal treated subjects (LD and HD treated subject, combined) was 1% (1/76 subjects), 3% (1/127 subjects) and 3% (1/156 subjects), respectively.*
  - *No subjects had low outlier CPK values in any of the treatment conditions of this safety dataset.*
  - *These results are generally consistent with results on mean increases of CPK in the HD OROS Pal treatment condition and numerically smaller mean increases observed in other Pal treatment conditions observed in this Phase I/IIa dataset, as previously described.*

- *The incidence of each of outliers on each of the following parameters conditions were generally greater than 1% but were often no greater than 2% in any given Pal treatment condition (unless otherwise specified) compared to an incidence of 0 subjects in the placebo condition:*
  - *High LDH (up to 4% in the "Other" Pal condition and 3% in the HD OROS Pal Condition),*
  - *High eosinophil count,*
  - *Low platelet count,*
  - *Low neutrophil count, and*
  - *Low phosphorous.*

Schizophrenia Phase I/IIa Trials.
Reviewer Comments. *Results of the Schizophrenia Phase I/IIa dataset were generally similar to those of the healthy subject Phase I/IIa dataset, previously described.*

2% (12/103) subjects in the HD OROS Pal condition were high CPK outliers compared to no Pal IR subjects (0/33 subjects) and no risperidone subjects (0/53 subjects).

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

See previous sections on ADOs and SAEs for clinically remarkable outliers. Also see section 7.1.3.3 for potentially clinically remarkable subjects, ADOs and/or SAEs.

The Incidence of Outliers on LFTs (based on results in N005 submission, provided by the sponsor upon request)

ALT or AST at 3 times greater than the ULN in Subjects with Normal Baseline Values:
The sponsor was asked to provide the incidence of LFT outliers in all Phase III trials that included a placebo-controlled DB phase (6-week Studies -301, -302, -303 through -305) using the following criterion. An outlier was defined as having 3 times greater than the upper limit of normal on ALT or AST values during treatment among subjects with normal baseline baseline values on these parameters and on bilirubin levels. The studies with small samples sizes of Pal and placebo treatment groups (Studies -301 and -302) failed to reveal any outliers using this criterion. The following table shows results of outliers, as provided by the sponsor (in a response submission, N005).

TLABHP: Number of Subjects with ALT or AST >3ULN During Double Blind Phase
(Study R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)
Normal baseline	260	104	176
>3xuln	2 (1)	3 (3)	1 (1)

Note: Percentages calculated with the number of subjects who had normal AST, ALT, and bilirubin values at double-blind baseline as denominator.

Table continued on next pagexx?
LFT Table, continued

TLABHP: Number of Subjects with ALT or AST >3ULN During Double Blind Phase
(Study R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Olanzapine 10 mg (N=364) n (%)
Normal baseline	198	185	88	290
>3xuln	0	0	2 (2)	16 (6)

Note: Percentages calculated with the number of subjects who had normal AST, ALT, and bilirubin values at double-blind baseline as denominator.

ALT or AST of greater than 8 times the ULN in Subjects with Normal Baseline Values:
Also upon request the sponsor identified any subjects with normal LFTs at baseline (ALT, AST and bilirubin) that later developed elevations in ALT and/or AST of greater than 8 times the ULN in the Phase III trials (the above listed Phase III trials, as well as for OL extension trials using the cut-off date of the more recent 120-Day Safety Update Report submission (submission was dated 2/1/06). There were no subjects meeting these criteria for the studies with small sample sizes for the Pal and placebo groups (Studies -301, -302) and for the OL Study -701 that also has a limited number of subjects relative to the larger OL trials, -702-705 (combined). Only 4 subjects met the outlier criteria among the Phase III trials.

The following is a line listing of LFT values for the 4 above subjects, as provided by the sponsor that in summary, showed transient, yet marked elevations in LFTs in the 3 subjects that continued on Pal treatment. The fourth subject was an ADO due to elevated LFTs on Day 22 of Olanzapine treatment. See reviewer comments below.

Study R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

OUTPUT sch2345 : Subjects Who had Normal ALT, AST, and Bilirubin at Baseline(DB) with AST or ALT of >8x Upper Limit of Normal Post Double Blind Baseline

Analysis Set: Safety

Subject Number	Age (years)	Sex	Country	Time Interval	Actual Date of Sample	Relative Day	ALT (U/L)	ALT >8x ULN	AST (U/L)	AST >8x ULN	BILIRUBIN (umol/l)	DIRECT BILIRUBIN (umol/l)	GGT (U/L)
Study Id: R076477-SCH-303/703 Treatment Group: Olan/Pali													
201609	23	FEMALE	RUSSIA	SCREENING(DB)	24JUN2004	-5	13		11		9	2	31
	23	FEMALE	RUSSIA	BASELINE(DB)	24JUN2004	-5						2	
	23	FEMALE	RUSSIA	BASELINE(DB)	29JUN2004	1	11		12		11		26
	23	FEMALE	RUSSIA	DAY 15(DB)	13JUL2004	15	22		18		5		20
	23	FEMALE	RUSSIA	DAY 43(DB)	11AUG2004	44	423	Yes	149		5	2	80
	23	FEMALE	RUSSIA	BASE(OPEN)	11AUG2004	1	423		149		5	2	80
	23	FEMALE	RUSSIA	WEEK 24(OPEN) *	18AUG2004	8	115		36		8	2	72
	23	FEMALE	RUSSIA	WEEK 24(OPEN)	08SEP2004	29						2	
	23	FEMALE	RUSSIA	WEEK 24(OPEN) *	08SEP2004	29	23		13		6		36
	23	FEMALE	RUSSIA	WEEK 24(OPEN)	26JAN2005	169	41		24		4		23
	23	FEMALE	RUSSIA	WEEK 52(OPEN)	08AUG2005	363	30		20		10	3	15
	23	FEMALE	RUSSIA	POST DAY 7(OPEN)	15AUG2005	370	17		16		5	2	14
Study Id: R076477-SCH-305/705 Treatment Group: Pali/Pali													
502015	32	MALE	UKRAINE	SCREENING(DB)	24FEB2005	-4	14		16		9	2	7
	32	MALE	UKRAINE	BASELINE(DB)	24FEB2005	-4	14		16		9	2	7
	32	MALE	UKRAINE	DAY 15(DB) *	01MAR2005	2	24		16		6		6
	32	MALE	UKRAINE	DAY 15(DB)	14MAR2005	15	46		20		4	2	9
	32	MALE	UKRAINE	DAY 43(DB)	12APR2005	44	428	Yes	200		7	3	17
	32	MALE	UKRAINE	BASE(OPEN)	12APR2005	1	428		200		7	3	19
	32	MALE	UKRAINE	WEEK 24(OPEN)	27SEP2005	169	89		43		4		17
Study Id: R076477-SCH-305/705 Treatment Group: Olan/Pali													
501368	24	MALE	UNITED STATES OF AMERICA	SCREENING(DB)	20AUG2004	-4	12		19		9	2	17
	24	MALE	UNITED STATES OF AMERICA	BASELINE(DB)	24AUG2004	1	10		16		9	2	16
	24	MALE	UNITED STATES OF AMERICA	DAY 15(DB)	07SEP2004	15	385	Yes	119				80
	24	MALE	UNITED STATES OF AMERICA	DAY 15(DB)	14SEP2004	22					7	2	
	24	MALE	UNITED STATES OF AMERICA	DAY 15(DB) *	14SEP2004	22	254		74				01
	24	MALE	UNITED STATES OF AMERICA	POST DAY 7(DB)	21SEP2004	29	45		18		7	2	59
Study Id: R076477-SCH-305/705 Treatment Group: Pali/Pali													
501558	48	FEMALE	UKRAINE	SCREENING(DB)	08NOV2004	-5	20		16		6	2	18
	48	FEMALE	UKRAINE	BASELINE(DB)	08NOV2004	-5						2	
	48	FEMALE	UKRAINE	BASELINE(DB)	11NOV2004	-2	25		18		5		16
	48	FEMALE	UKRAINE	DAY 15(DB)	26NOV2004	14	19		17		7		13
	48	FEMALE	UKRAINE	DAY 43(DB)	24DEC2004	42	25		23		7		18
	48	FEMALE	UKRAINE	BASE(OPEN)	24DEC2004	1	25		23		7		18
	48	FEMALE	UKRAINE	WEEK 24(OPEN)	07JUN2005	166	373	Yes	186		11	2	15
	48	FEMALE	UKRAINE	WEEK 24(OPEN) *	15JUN2005	174	443		72		10	2	18
	48	FEMALE	UKRAINE	WEEK 52(OPEN)	20DEC2005	362	17		19		9	2	7
	48	FEMALE	UKRAINE	POST DAY 5(OPEN)	28DEC2005	370	17		25		15	2	7

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Reviewer Comment

Elevations during Pal treatment were transient in the subjects revealed in the special search even in subjects that had Pal dose-levels increased, as LFT values declined or normalized (upon review of the narratives for the above subjects provided in the original NDA submission and in the SUR, as well as in the sponsor's response submission N005). One subject also had a history of viral hepatitis (501558).

An olanzapine subject was withdrawn on Day 22 (subject 501268) due to elevated LFTs in which values normalized at 7 days after the last dose. Since study drug was not continued in this subject it is not known if values would have eventually normalized with continued treatment, as observed among the Pal subjects described above. It is also noteworthy that olanzapine subjects showed the largest incidence of outliers on ALT or AST of greater than 3 times the ULN (in subjects with normal baseline values) which was 6% compared to only 1% of placebo subjects and 0-3% of subjects in Pal groups (as previously shown for the short-term Phase III trial, combined, dataset). Approved labeling for olanzapine describes transient elevations in LFTs under the Precautions section of labeling.

Also see previous sections on ADOs and SAEs in this review. One ADO due to elevated LFTs is described that appear to be drug-related transient and remarkable elevations of LFTs (of up to approximately 8 times the ULN) in Subject 503018. as previously described in this review. Pal

treatment was discontinued while LFTs were markedly elevated. Consequently, it is not clear if these elevations would have normalized spontaneously with continued Pal treatment. Despite this uncertainty, elevations to this degree are clinically remarkable and warrant cessation of treatment.

See Section 7.1.3.3 for additional potentially clinically remarkable subjects with abnormal LFT values.

See additional comments and recommendations in the last section of this review.

7.1.7.4 Additional analyses and explorations

See the previous subsection.

7.1.7.5 Special assessments

7.1.7.5.1 Results on Prolactin Levels

Reviewer Comments on Prolactin Results *Appendix 2.7.4.4.1.1 was found to contain some results on prolactin levels for some safety datasets. A drug class effect of increasing prolactin levels is well known. However, the following observations are notable findings:*

- *Dose dependent group mean increase was observed with OROS Pal in which little to no increase was revealed with a 3 mg daily dose of OROS Pal (similar to the placebo group), while a remarkable group mean increase was observed at the 6, 9, 12 and 15 mg daily dose-level groups in the 3-Phase III safety dataset. See results in the summary table below.*
- *The above results also revealed large group mean increases in Prolactin for each of the daily Pal dose levels of above the lowest dose level (in the 6, 9, 12 and 15 mg daily dose groups, but not in the placebo or 3 mg groups) that were remarkably greater than that observed for the olanzapine group (10 mg/daily). See results in the summary table below.*
- *Phase I/IIa results (schizophrenia trials) revealed similar mean Prolactin level increases in Pal groups (OROS and non-OROS groups compared) to Risperidone treatment (mean levels of 32.1 and 37.0 ng/ml were observed in the high dose OROS Pal and the risperidone groups, respectively.*
- *See section 7.1.4 for results showing a numerically greater incidence of potentially prolactin-related AEs in the 12 and 15 mg Pal groups compared to only a few to no reported AEs in the lower dose Pal groups, the Olanzapine group and the placebo group (revealed in the 3-Phase III trial dataset).*

Results on Prolactin Levels (copied from pages 3136-3138 of an appendix to the SCS)

Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305

Output DLAB01: Laboratory Values: Means and Mean Changes Over Time - Double-Blind Phase (continued)

Analysis Set: Safety

							Base	change from baseline					
	N	Mean	SD	Med	Min	Max	Mean (SD)	N	Mean	SE	SD	Med	Min	Max
PROLACTIN (ng/ml)														
Placebo														
SCREENING	352	35.73	42.452	19.00	2.1	279.3								
BASELINE	355	20.69	30.564	11.43	1.1	257.1								
DAY 15	329	15.33	17.376	10.68	1.2	137.3	20.44 (30.537)	329	-5.11	1.567	28.421	-0.96	-243.8	81.8
DAY 36	146	15.23	21.424	9.66	1.0	169.4	21.90 (36.105)	146	-6.67	3.037	36.694	-1.16	-227.2	149.5
DAY 43	134	14.17	20.128	9.30	1.0	160.8	20.07 (29.976)	134	-5.90	2.647	30.641	-1.21	-226.4	144.9
END POINT	331	15.41	17.832	10.19	1.0	160.8	20.67 (30.840)	331	-5.26	1.632	29.685	-1.15	-226.4	144.9
ER OROS PAL 3 mg														
SCREENING	124	46.65	66.731	24.95	3.4	385.3								
BASELINE	126	27.65	57.413	12.23	0.9	446.4								
DAY 15	121	62.92	68.442	37.94	4.5	473.8	28.56 (58.689)	120	34.66	5.979	65.492	23.37	-260.0	436.9
DAY 36	73	64.71	83.056	33.47	3.5	548.9	27.30 (66.439)	72	37.95	9.435	80.062	22.14	-174.5	512.1
DAY 43	67	66.01	101.489	32.72	4.5	750.4	24.27 (54.746)	66	42.30	13.011	105.704	19.61	-248.0	713.6
END POINT	121	60.83	84.577	32.68	4.5	750.4	28.56 (58.689)	120	32.54	8.154	89.322	19.51	-248.0	713.6
ER OROS PAL 6 mg														
SCREENING	234	37.70	48.124	19.25	1.1	330.1								
BASELINE	234	22.62	34.649	12.04	1.2	381.8								
DAY 15	218	72.40	62.473	52.51	2.9	479.2	22.48 (34.723)	217	50.24	3.552	52.326	37.82	-48.0	279.6
DAY 36	125	67.79	58.432	50.81	4.4	334.9	20.68 (28.174)	125	47.11	4.561	50.992	30.71	-83.3	285.1
DAY 43	125	66.10	57.905	49.70	4.5	350.3	20.78 (28.429)	125	45.32	4.553	50.904	31.96	-90.7	286.1
END POINT	218	67.35	61.153	48.15	1.2	364.9	22.48 (34.723)	217	45.18	3.421	50.401	31.57	-90.7	286.1
ER OROS PAL 9 mg														
SCREENING	239	43.14	55.038	23.17	1.8	455.2								
BASELINE	245	25.15	43.343	11.18	1.4	426.1								
DAY 15	235	85.16	69.238	60.84	5.9	489.2	25.24 (43.624)	234	60.12	4.006	61.277	40.82	-68.2	300.3
DAY 36	157	84.09	96.490	53.85	4.7	989.3	22.84 (35.918)	157	61.25	7.413	92.885	39.78	-37.7	973.5
DAY 43	158	83.15	61.602	59.40	3.4	278.1	23.90 (37.766)	158	59.25	4.979	62.584	40.49	-57.5	255.4
END POINT	235	76.14	59.756	51.76	3.4	297.3	25.24 (43.624)	234	51.06	3.823	58.473	35.79	-128.8	255.4
ER OROS PAL 12 mg														
SCREENING	239	38.72	49.554	20.57	2.0	300.2								
BASELINE	241	23.28	35.466	12.43	1.6	261.6								
DAY 15	230	88.09	64.191	68.13	5.4	325.3	22.74 (33.378)	230	65.35	3.820	57.933	48.85	-77.9	293.6
DAY 36	147	80.49	62.315	62.11	5.6	379.0	19.98 (28.584)	147	60.51	4.438	53.814	39.85	-39.5	218.7
DAY 43	151	81.68	62.961	62.83	2.4	344.8	22.59 (35.515)	150	58.93	4.473	54.789	42.30	-52.6	253.6
END POINT	232	77.03	62.026	56.93	2.4	344.8	22.81 (33.326)	231	54.09	3.662	55.664	39.42	-77.9	253.6
ER OROS PAL 15 mg														
SCREENING	112	33.98	37.665	22.07	2.4	269.3								
BASELINE	113	19.36	21.898	12.22	1.1	136.1								
DAY 15	108	92.00	67.450	71.24	8.3	303.4	19.61 (22.219)	108	72.37	6.110	63.500	59.53	-31.4	284.8
DAY 36	78	90.34	67.495	66.33	7.2	318.3	19.58 (23.205)	78	70.75	7.117	62.854	50.63	-8.9	256.2
DAY 43	79	85.98	62.485	67.78	7.4	286.5	17.73 (18.636)	79	68.25	6.805	60.485	52.30	-29.9	253.8
END POINT	110	80.92	61.181	63.31	5.5	286.5	19.53 (22.072)	110	61.39	5.568	58.399	44.33	-31.4	253.8
Total Paliperidone														
SCREENING	948	40.06	52.031	21.09	1.1	455.2								
BASELINE	959	23.71	39.709	12.02	0.9	446.4								
DAY 15	912	80.71	66.639	58.45	2.9	489.2	23.72 (39.650)	909	57.18	1.997	60.198	39.99	-260.0	436.9
DAY 36	580	78.07	75.891	53.68	3.5	989.3	21.76 (36.670)	579	56.39	2.948	70.931	37.28	-174.5	973.5
DAY 43	580	77.50	67.383	56.65	2.4	750.4	22.08 (35.729)	578	55.45	2.703	64.981	39.07	-248.0	713.6
END POINT	916	72.83	64.782	51.34	1.2	750.4	23.72 (39.593)	912	49.24	2.034	61.438	34.77	-248.0	713.6
Olanzapine 10 mg														
SCREENING	361	39.50	55.231	20.48	1.4	361.1								
BASELINE	364	21.84	34.632	11.33	1.3	324.4								
DAY 15	344	23.41	30.496	16.14	1.9	290.4	22.04 (35.474)	344	1.37	1.657	30.725	3.09	-204.6	248.5
DAY 36	226	21.67	30.228	14.06	2.0	359.0	24.75 (41.859)	226	-3.08	2.396	36.019	1.58	-294.9	158.1
DAY 43	216	19.93	25.124	14.33	2.8	290.6	24.36 (40.456)	216	-4.43	2.349	34.522	2.05	-313.8	89.7
END POINT	352	19.39	21.860	14.21	2.0	290.6	21.98 (35.135)	352	-2.59	1.636	30.703	2.42	-313.8	89.7

7.1.8 Vital Signs

A Caveat on Group and Time-point Comparisons on a Given Clinical Parameter. *Results of statistical group or time-point comparisons or in-text description of statistical results on clinical parameters could not be found in the SCS. Therefore, group and time-point comparisons described in this review on any given clinical parameter are based on numerical comparisons, unless otherwise specified (results on clinical parameters that were found in the SCS and are described in this review did not include statistical comparisons).*

7.1.8.1 Overview of vital signs testing in the development program

The outlier criteria for vital signs is provided in the Table 10.2 in the appendix of this review, as provided by the sponsor.

Vital signs were obtained at multiple time-points during the Phase III and OL trials. Refer to the schedule of assessments in Table series 10.1 in the appendix of this review for the study schedules of Phase III trials.

Reviewer Comments of Vital Sign Methods. *Vital signs were conducted daily from Days 1-6 and then on selected Days for the remainder of the DB trials and OL trials.*

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See the previous subsection and sections below. Also refer to Section 7.1 for a description of integrated datasets analyzed and described in this review.

7.1.8.3 Standard analyses and explorations of vital signs data

See the next subsection below.

7.1.8.3.1. Analyses focused on measures of central tendencies

Completed Phase III Non-Elderly Trials -303, -304 and -305.
Reviewer Comments. *Descriptive statistical results were found in Appendix 2.7.4.5.1.1 of the SCS (time-points examined were: baseline, days 2, 3, 4, 5, 6, 8, 15, 22, 29, 36, 43 and endpoint).*

A Caveat: *one critical caveat to interpreting vital sign results is that the window of time shown below for each scheduled assessment (copied from the submission):*

Variable	Scheduled Visit Number	Time Interval (Label on ouput)	Time Interval (Day)[a]	Target Time Point (Day)

Vital Signs	1,2	Baseline	<1	1
	3	Day 2	2	2
	3	Day 3	3	3
	4	Day 4	4	4
	4	Day 5	5	5
	4	Day 6	6	6
	5	Day 8	7-11	8
	6	Day 15	12-18	15
	7	Day 22	19-25	22
	8	Day 29	26-32	29
	9	Day 36	33-39	36
	10	Day 43	40-end of DB	43

[a] Relative to the first day of double-blind study drug administration
[b] Time point will be assessed based on the scheduled elapsed time (EGPTMNUM) in the data set.
[c] Applicable to all laboratory tests except for prolactin.
[d] Only for prolactin that is assessed at Day 36.

Subjects were inpatients for the first 2 weeks of DB treatment but could be discharged thereafter. Between subject variance on the timing of assessments and relative to dosing (between subject variance on timing of dosing) is likely to be greatest on outpatient assessments days. However, the days that examined PK (with multiple blood samples collected on a give study day) would be anticipated to have the timing of assessments more tightly controlled (in which subjects would have to be a the study site or inpatients during this procedure) than on study days that did not involve multiple blood sample collections on the given day.

Another Caveat on Group and Time-point Comparisons on a Given Clinical Parameter. *Results of statistical group or time-point comparisons or in-text description of statistical results on clinical parameters could not be found in the SCS. Therefore, group and time-point comparisons described in this review on any given clinical parameter are based on numerical comparisons, unless otherwise specified (results on clinical parameters that were found in the SCS and are described in this review did not include statistical comparisons).*

A Summary of the Results
Due to the lengthiness of the summary table of vital sign results (37 pages long for the summary table, Appendix 2.7.4.5.1.1 of the SCS) this review summarizes the results of this table, rather than showing the results shown in the 37 page table.

The descriptive statistical results on vital sign parameters generally failed to show any new or clinically remarkable findings other than a few potential exceptions. Key observations are outlined below (the below items include potentially unexpected or new findings, whole noting some relevant negative findings for a clinically remarkable effect on a given parameter):

- *A mean increase from baseline in supine tachycardia was observed that was time-dependent and dose-dependent with greatest effects generally observed in the HD group (15 mg). The maximum mean increase observed in this group was 6.8±12.9 bpm on Day 6 (ranging up to a maximum individual-subject increase of 128 bpm in this group at this time-point).*

- *The placebo group generally showed little to no change at each time point (mean change from baseline to Day 6 was 0.6±11bpm).*
- *The Olanzapine group showed little to no change in this parameter compared to all Pal groups. It is important to note the large variance (SD) from a statistical standpoint. See previous discussions regarding this observation of a drug-induced increase in supine heart rate.*
- *Refer to the last section of this review for additional comments and recommendations.*

- *Another potentially unexpected finding that could be considered a real dose-dependent effect or could be an isolated finding (e.g. a false positive) is a slight mean increase (from baseline to DB treatment time-points) in supine systolic blood pressure (sBP) that was only observed in the HD Pal group (15 mg) during the first week of treatment (a group mean increase of up to 4.± 12.9 mmHg on Day 5). The lower-dose Pal groups and the placebo group generally showed no mean change in sBP at any given time-point (mean changes were generally within -1 to 1 mmHg for any given group at any given time-point).*
- *Mean changes in standing to supine (standing-supine) blood pressure (systolic and diastolic) failed to show any clinically remarkable findings in which the greatest mean change from baseline at any given time-point for sBP was generally in the HD group (15 mg Pal) which only showed a mean change of -2.5±11.8 mmHg on Day 5.*
- *Standing-supine mean changes on heart rate failed to show any remarkable mean or median changes at any given time-point in any given treatment group. The HD (15 mg) group showed mean changes of 1.3 to -0.5 bpm (±9 to 13).*
- *Results on standing heart rate showed dose-dependent and time-dependent mean increases from baseline as follows:*
  - *The HD Pal group generally showed higher mean increases of up to 7 bpm (SD of ±14 or ±15) on Days 3 and 4 (a mean increase of 5 to 6 were observed on Days 2, 5, 6 and 8) that appeared to be greater in magnitude and longer in duration over treatment than the mean increases observed in lower dose Pal groups (based on numerical comparisons) with little to no change in the placebo group (mean change of 1.5 to -0.8 observed in the placebo group).*
  - *The magnitude of these peak mean increases observed on Days 3 and 4 in the HD group appeared to be become increasingly smaller with each subsequent time-point. That is, the peak effect observed early in treatment (Days 3 and 4) appeared to diminish over time over Days 5 though Day 36 of treatment with a mean change of only 0.5 observed on the final on-treatment assessment day (Day 43).*
  - *The placebo group showed no mean increases from baseline to each time-point on standing heart rate (mean changes were generally less than 1 bpm).*
  - *Surprisingly, the olanzapine group (10 mg/day) generally showed no to little mean changes at any given time-point (similar to the placebo group), whereas even the lowest Pal group (3 mg) consistently showed mean increases in standing heart rate for all time-points that appeared to persist up to approximately Day 22 (a mean change of up to 4.4 was observed on Day 2 in this low dose group).*

- *Mean increases were generally observed for all time-points during the first 2-3 weeks of treatment in all Pal groups.*

Caveat on Phase III results on BP and Timing of Assessments Relative to Dose, PK and other Potential Time-dependent Confounding Variable and Relative to Fed Versus Fasted Conditions.

The sponsor was asked to provide data for vital sign results near Tmax ideally from a schizophrenia trial but the Phase III trials and the QT prolongation study, Trial –SCH-1009 did not include assessments at multiple time-points in order to enhance capturing Tmax or other time-dependent confounding variables. Study -1009 only included baseline and end-of-study vital sign assessments (this study is described under Section 7.1.12). The sponsor provided results of Study SCH-1009 in response to this inquiry which is described in Section 7.1.13 but had a limited number of subjects and used 3 and 6 mg dose-levels. Also vital signs were only conducted at pre-dose, 24 and 48 hour post-dose time-points on selected treatment days.

Therefore, the undersigned reviewer describes results of 2 food effect Phase I studies (P01-1008 found in the N000 submission and P01-1002 found in the 210-Day SUR submission). See Section 7.1.12 C for additional vital sign and related observations from these trials.

See section 7.1.3.3.E for a description of individual potentially clinically remarkable subjects.

Summary of Results on Temperature in Phase III Trials:

***A Caveat:** Temperature results were found for a subgroup of subjects within any treatment group during the DB treatment phase with samples sizes being insufficient for most on-treatment time-points except for Day 43 in which the sample size for any given group was generally over 150 subjects. The study end-point assessments generally had larger samples sizes of over 200 subjects in most group. The 15 mg Pal group only had 79 subjects on Day 43 and 104 subjects at end-point for this vital sign parameter.*

Given the small samples sizes for most time-points in each treatment group this review only describes temperature results for Day 43 and study end-point assessments relative to baseline values.

Given the above critical caveat on the limitations of the data, the temperature results were unremarkable including results of the HD Pal group which showed a mean change of only 0 to -0.02±0.5 degrees C from baseline on Day 43 and study end-point.

Results on Respiratory Rate in Phase III trials
These results were not generally found, yet, such results in a Phase III trial study are generally non-revealing (fail to show or reveal an effect). Refer to Sections on SAEs and ADOs and Section 7.1.3.3 of this review for potentially clinically remarkable events that involved the respiratory system.

Refer to the last section of this review for additional comments and for recommendations.

Results of the Completed Elderly Phase III Trial (-302)

Summary of Results as described in Section 6.5.1 of the CSR and based on a review of vital sign results found in a 10-page table in Attachment 9.1.1 of the CSR, that was hyperlinked from the SCS (rather than showing a 10-page table the results are summarized in this review):

- *These results failed to reveal any new, clinically remarkable findings other than the following bulleted item.*
- *Greater effects on increased supine and standing HR appeared to exist in older subjects (70-75 year old) compared to younger subjects (64-69 year old) that persisted until treatment endpoint in the older group*

Refer to the last section of this review for additional comments and recommendations.

Results of Ongoing Phase III Open-Label Extension Studies (-702 through -705)
Results of the following treatment groups were reviewed in the sponsor's summary table in Appendix 2.7.4.5.1.2 of the SCS which showed descriptive statistical results during the DB phase of the lead-in studies, as well as during the OL phase of the extension trials for the pooled dataset for each treatment subgroup.

Due to the lengthiness of the sponsor's summary table (69 pages) the results are summarized below rather than providing a lengthy summary table in this review.

Caveats
Each treatment subgroup had sample sizes for vital sign assessments that ranged from only a few subjects to generally less than 50 subjects at time-points beyond week 4 of OL treatment for the ≤ 3month subgroups and beyond week 24 for the > 3 month subgroups (the treatment subgroups were: DB-placebo/OL-Pal, DB-Olanz/OL-Pal, DB-Pal/OL-Pal treatment groups).

- *The ≤ 3 month "total" Pal group (all subjects in the OL phase who participated in the OL study for > 3 months) had sample sizes of over 50 subjects for all time-points through Week 40.*
- *Only the time-points of these subgroups that had at least 50 subjects were reviewed and described below (since smaller samples sizes were generally considered insufficient for the purposes of this review).*

Comments and description of observations below are based on numerical comparisons (statistical comparison results could not be found in the sponsor's summary table or in-text tables or descriptions in the SCS).

Summary of Results
The results of this safety dataset were generally unremarkable for revealing any new, clinical significant drug effects on vital sign parameters except for results described below that may provide some potentially new clinically relevant observations.

Similar to that observed for the short-term trial dataset, a mean increase (from baseline) in standing heart rate was observed during treatment. This positive result is not unexpected. However, observations on the timing of peak effects and the duration of this effect during longterm treatment are potentially new such that a discussion of these results is warranted.

Similar observations for a drug-induced increase in supine heart rate (which was observed in short term trials) also warrant some discussion with respect to timing of peak effects and the duration of this effect.

Key findings are noted, as follows:

- *Peak mean increases in standing heart rate were generally observed within approximately one week of OL Pal treatment or DB olanzapine treatment. This known drug-class effect either persisted at a smaller magnitude on subsequent time-points during treatment or this effect appeared to resolve by approximately 4 weeks in most subgroups examined. See the paragraphs that follow these bulleted items for a more detailed description of these results.*
- *Subjects started on DB olanzapine treatment in the short-term lead-in studies also showed the expected drug-induced mean increase in standing heart rate that also appeared to resolve during DB olanzapine treatment.*
- *This known drug-class effect on standing heart rate appeared to return after switching subjects from Olanzapine to OL Pal in the OL extension trials following completion of the short-term DB lead-in studies. Perhaps this apparent recurrence of a drug-induced effect on standing heart rate reflects an interruption of treatment between the DB lead-in and OL extension trials. Yet this effect does not appear to exist for the DB Pal/OL Pal treatment group (examine ECG HR results provided in this review under Section 7.1.9 which shows this phenomenon). Consequently, this observation could be reflecting a differential drug or dose-level effect between olanzapine and Pal treatment. See the paragraphs that follow these bulleted items for a more detailed description of these results. Also see the final section of this review for additional comments and recommendations.*
- *Supine heart rate showed a peak mean increase from baseline of up to 5.5 bpm on Day 4 and 4.2 bpm on Day 4 in the DB-Placebo/OL-Pal ≤ 3month and > 3 month subgroups, respectively. This drug effect appeared to persist over time. However, the magnitude of this effect did not appear to increase over time. Similar results were observed for other treatment subgroups in this OL extension trial safety dataset.*
- *DB Olanzapine treatment showed similar effects on increasing supine heart rate (in the DB Olanzapine/OL Pal subgroups) that appeared to resolve within approximately 2 weeks. As observed with standing heart rate, the drug-induced increase in supine heart rate appeared to return upon switching these subjects to OL Pal. Again, these observations may reflect an interruption of antipsychotic treatment between the DB lead-in and OL extension trials. However, subjects were to have DB treatment abruptly*

terminated before entering into the OL phase. Alternatively, this observation could be reflecting a differential drug or dose-level effect between olanzapine and Pal treatment.

While the interpretation of OL results is limited by the absence of a placebo control group, the above findings were observed in the direction of an expected drug-effect (e.g. increases in heart rate instead of decreases in heart rate), whereby the results are strongly suspicious of a read Pal induced effect.

See the final section of this review for further comment and recommendations.

The following outline provides more details on the above results on drug-induced mean increases in standing heart rate over time (during OL Pal and DB olanzapine treatment:

- *A mean increase from baseline in standing heart rate of up to 5.9 bpm and 5.6 bpm in the ≤ 3 month and > 3 month subgroups, respectively, of the DB-placebo/OL-Pal treatment group was observed by week 1 of OL treatment (with little to no change during DB placebo treatment in these two subgroups).*
- *Other subgroups generally showed similar results, including results during DB olanzapine treatment during the lead-in phase followed by OL pal treatment.*
- *This mean increase generally appeared to persist, but with an apparent smaller magnitude of effect over subsequent OL time-points or the effect appeared to resolve by approximately 4 weeks of treatment (for time-points that had a sample size of at least 50 subjects).*

The following is a more detailed discussion of standing heart rate increases when switching from DB Olanzapine to OL Pal treatment:

- *DB olanzapine treatment (in the DB-Olanzapine/OL-Pal exposure subgroups) showed a peak mean increase of 2.7 bpm on Day 4 and Day 6 for each of the ≤ 3 month and > 3month exposure-subgroups, respectively.*
- *Little to no change (from baseline) in standing heart rate was observed after the first few weeks of DB Olanzapine treatment, such that Olanzapine induced increased heart rate appear to resolve over time.*
- *After being switched from DB Olanzapien to OL Pal, these subjects showed an apparent recurrence in antipsychotic-induced increased in heart rate. The peak mean increase observed during OL Pal treatment in these subjects was 5.2 bpm on Day 4 for the ≤ 3 month subgroup and 3.3 bpm on week 1 in the > 3 month group. This drug effect appeared to resolve by approximately 4 weeks or less.*
- *It is not clear why a recurrence of a drug class effect would occur when switching from one drug to another within the same drug class. Perhaps treatment was interrupted between the DB lead-in and OL extension trials or this observation could be reflecting a differential drug or dose-level effect between olanzapine and Pal treatment. Yet, this phenomenon was not observed in the DB pal/OL Pal subgroup (refer to heart rate data shown under section 7.1.9 on ECG results that shows the same pattern on this heart rate determined by ECG).*

7.1.8.3.2. Analyses focused on outliers or shifts from normal to abnormal

Completed Phase III Trials -303, -304 and -305.

Reviewer Comments.

An important positive finding in the pooled short-term Phase III trial dataset was a greater incidence of outliers for increased supine heart rate in paliperidone groups. While a consistent dose-dependent effect on the incidence of outliers was not observed in this safety dataset, the greatest incidence of outliers was in the highest dose group (22% in the 15 mg group compared to 10% in placebo subjects and 15 to 18% in each lower dose Pal group).

Evidence for orthostatic hypotension was revealed, which is an expected finding based on that which is known and described in labeling for Risperdal® and other approved drugs in this drug class. Refer to section 7.1.4 for reviewer comments and description of results that were found in a separate section of the SCS (section 2.1.6.5 in the SCS). Results are provided in this section of this review, for the convenience of the reader.

The Incidence of Outliers on Vital Sign Measures

Table 76: Number of Subjects With Abnormal Vital Sign Values During the Double-Blind Period (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) N (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
Standing pulse classification	353	126	234	245	240	113	958	363
Decrease ≥15 and value ≤50	1 (<1)	0	0	2 (1)	2 (1)	1 (1)	5 (1)	3 (1)
Increase ≥15 and value ≥100	77 (22)	42 (33)	61 (26)	72 (29)	75 (31)	44 (39)	294 (31)	88 (24)
Supine pulse classification	353	125	234	245	241	113	958	363
Decrease ≥15 and value ≤50	6 (2)	1 (1)	1 (<1)	6 (2)	4 (2)	3 (3)	15 (2)	5 (1)
Increase ≥15 and value ≥100	35 (10)	23 (18)	33 (14)	45 (18)	36 (15)	25 (22)	160 (17)	42 (12)
Standing SBP classification	353	126	234	245	241	113	959	363
Decrease ≥20 and value ≤90	12 (3)	8 (6)	7 (3)	16 (7)	13 (5)	7 (6)	51 (5)	13 (4)
Increase ≥20 and value ≥180	4 (1)	0	3 (1)	1 (<1)	0	1 (1)	5 (1)	1 (<1)
Supine SBP classification	352	125	234	245	241	113	958	363
Decrease ≥20 and value ≤90	12 (3)	6 (5)	4 (2)	16 (7)	4 (2)	6 (5)	36 (4)	12 (3)
Increase ≥20 and value ≥180	4 (1)	0	3 (1)	1 (<1)	1 (<1)	1 (1)	6 (1)	0
Standing DBP classification	353	126	234	245	241	113	959	363
Decrease ≥15 and value ≤50	7 (2)	3 (2)	6 (3)	1 (<1)	5 (2)	2 (2)	17 (2)	9 (2)
Increase ≥15 and value ≥105	13 (4)	2 (2)	6 (3)	7 (3)	4 (2)	2 (2)	21 (2)	16 (4)
Supine DBP classification	352	125	234	245	241	113	958	363
Decrease ≥15 and value ≤50	6 (2)	0	9 (4)	3 (1)	4 (2)	2 (2)	18 (2)	11 (3)
Increase ≥15 and value ≥105	7 (2)	0	2 (1)	2 (1)	4 (2)	4 (4)	12 (1)	8 (2)

Note: Percentages calculated with the number of subjects per parameter as denominator.

The sponsor notes that the above findings on increased heart rate are consistent with the incidence of AEs of tachycardia observed with this dataset (as previously described in Section 7.1.5) which was reported in 12% of Pal subjects compared to 7% of placebo subjects.

The sponsor also notes that 5 SAEs and 5 ADOs of tachycardia or sinus tachycardia were observed in this safety dataset. See Sections 7.1.3.1 and 7.1.3.2 on SAEs and ADOs and Section 7.1.3.3 of this review.

Upon review of the CSR for this study, Section 6.5.1 indicates no ADOs and SAEs due to orthostatic hypotension.

According to Section 6.5.1 of the CSR there also no SAEs or ADOs due to hypotension. However, a greater incidence of AEs of hypotension were reported in Pal compared to placebo subjects (5% and 0%, respectively) and subject 2007010 is described as having "severe" hypontesion on Day 40 after receiving her last Pal dose (9mg) on the previous day. This subject was hospitalized for pneumonia and pleural effusion. *In the opinion of the undersigned these events could at least in part be drug-related.* Three additional subjects had AEs of "moderate" hypotension of whom each received 6 mg, 9 mg and inadvertently 15 mg Pal, respectively, at the time of this AE (subjects 200309, 200702 and 200625, respectively).

A description or notation of any other SAEs or ADOs due to abnormal vital sign parameters, could not be found in sections in the SCS related to this topic. However, potentially clinically remarkable subjects relevant to abnormal vital sign parameters (e.g. outliers for high blood pressure values) were found by the undersigned reviewer upon review of line listings, narratives or CSRs, as described under Section 7.1.3.3 of this review.

Table 52: Number of Subjects With Treatment-Emergent Orthostatic Hypotension at Any Time During the Double-Blind Period
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
Total no. subjects with orthostatic hypotension	14 (4)	10 (8)	13 (6)	23 (9)	9 (4)	12 (11)	67 (7)	15 (4)
Pulse(std-sup) > 15 and SBP(std-sup) < -20	11 (3)	8 (6)	7 (3)	18 (7)	5 (2)	8 (7)	46 (5)	11 (3)
Pulse(std-sup) > 15 and DBP(std-sup) < -10	10 (3)	5 (4)	12 (5)	12 (5)	7 (3)	8 (7)	44 (5)	7 (2)

Note: Percentages calculated with the number of subjects in each group as denominator.

Results on Outliers found in a Separate Section 2.1.6.5 of the SCS

Table 52: Number of Subjects With Treatment-Emergent Orthostatic Hypotension at Any Time During the Double-Blind Period
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
Total no. subjects with orthostatic hypotension	14 (4)	10 (8)	13 (6)	23 (9)	9 (4)	12 (11)	67 (7)	15 (4)
Pulse(std-sup) > 15 and SBP(std-sup) < -20	11 (3)	8 (6)	7 (3)	18 (7)	5 (2)	8 (7)	46 (5)	11 (3)
Pulse(std-sup) > 15 and DBP(std-sup) < -10	10 (3)	5 (4)	12 (5)	12 (5)	7 (3)	8 (7)	44 (5)	7 (2)

Note: Percentages calculated with the number of subjects in each group as denominator.

Results from Elderly Study -302.

Reviewer Comment. *Results of Study -302 were generally similar to those of the pooled short-term Phase III dataset of primarily non-elderly subjects (as previously described). However, one potentially new finding (not observed in the primarily non-elderly, short-term trials) was the following observations:*

- *A numerically greater incidence of outliers on increased supine systolic BP and decreased supine systolic BP were observed in Pal compared to placebo subjects. The outliers occurred in only 4 or 5 out of the 76 Pal subjects. Given the small sample size of this study (only 38 placebo subjects and 76 Pal subjects), these findings are considered preliminary.*

Upon review of the CSR for Study -302, the following additional findings were noted in Section 6.3.2.4.3 of the CSR:

- *One subject (200234) developed tachycardia on Day 5 of Pal treatment who later was found to have supraventricular tachycardia on Day 29. More information (e.g. ECG results) could not be found in the in-text CSR description or in in-text sections of the SCS.*
- *No ADOs or SAEs of tachycardia occurred in Pal subjects of this study.*
- *12 Subjects had an AE of tachycardia as follows:*
  - *9 out of 12 Pal subjects with the AE of tachycardia had this event reported within 2 weeks of treatment.*
  - *The other 3 subjects had this AE reported on Days 33, 36 or on both Days 9 and 42, respectively.*
  - *The lowest dose level of Pal among these 12 Pal subjects was 6 mg daily and the mean dose at the onset of the AE was 8.5 mg daily among these subjects.*

- *The incidence of preexisting medical conditions in these 12 subjects was 67% and 42% for cardiovascular or cerebrovascular disease, respectively compared to an incidence of 38% and 16% in Pal subjects who did not have the AE of tachycardia.*

The findings on concomitant illness are considered preliminary, given the small sample size and post hoc analyses. It is also not known if the above observations are reproduceable.

See the final section of this review for comments and recommendations.

Results on the incidence of orthostatic hypotension outliers were previously described under Section 7.1.4 (found in a separate section in the SCS). Refer to section 7.1.4 for reviewer comments and description of results.

The sponsor's summary table found in a separate section 2.1.6.5 in the SCS is provided below for the convenience of the regulatory supervisor reading of this review.

Also refer to Sections 7.1.1-3 of this review for additional information (SAEs and ADOs and a description of potentially remarkable subjects with cardiovascular related events).

The table below summarizes the vital sign results (as provided by the sponsor).

Table 77: Subjects With Abnormal Vital Sign Values During the Double-Blind Period
(Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)
Standing pulse classification	38	76
Decrease ≥15 and value ≤50	0	0
Increase ≥15 and value ≥100	2 (5)	9 (12)
Supine pulse classification	38	76
Decrease ≥15 and value ≤50	0	0
Increase ≥15 and value ≥100	0	5 (7)
Standing SBP classification	38	76
Decrease ≥20 and value ≤90	2 (5)	7 (9)
Increase ≥20 and value ≥180	0	4 (5)
Supine SBP classification	38	76
Decrease ≥20 and value ≤90	1 (3)	4 (5)
Increase ≥20 and value ≥180	0	3 (4)
Standing DBP classification	38	76
Decrease ≥15 and value ≤50	3 (8)	4 (5)
Increase ≥15 and value ≥105	0	0
Supine DBP classification	38	76
Decrease ≥15 and value ≤50	1 (3)	1 (1)
Increase ≥15 and value ≥105	0	1 (1)

Note: Percentages calculated with the number of subjects per parameter as denominator.
Cross-reference: Mod5.3.5.1/R076477-SCH-302/Sec6.5.1

Results on Orthostatic Hypotension Outliers found in a Separate Section 2.1.6.5 of the SCS

Table 53: Number of Subjects With Treatment-Emergent Orthostatic Hypotension at Any Time During the Double-Blind Phase (Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)
Total no. subjects with orthostatic hypotension	0	3 (4)
Pulse (std-sup) > 15 and SBP (std-sup) < -20	0	2 (3)
Pulse (std-sup) > 15 and DBP (std-sup) < -10	0	1 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Mod5.3.5.1\R076477 SCH 302\Sec6.5.1.

Results from Pooled Open Label Extension Trial Dataset (Studies -702 through -705).
Reviewer Comment. *Only 0-6% of subjects in the OL trial dataset (all subjects received Pal) met outlier criteria for supine or standing, diastolic or systolic BP changes, while 10 to 25% of subjects had increased standing or supine heart rates. These observations suggest that tachycardia or increased heart rate (supine or standing) can occur in some subjects, in the absence of clinically remarkable orthostatic decreases in blood pressure. However, this observation is not considered conclusive evidence for increased heart rate in the absence of a drug effect on blood pressure since comparisons on the incidence of outliers across parameters depends on the cut-off values selected.*

SAEs and ADOs due abnormal vital signs that included tachycardia are previously discussed (see Sections 7.1.3.1 and 7.1.3.2 of this review).

Results on the incidence of orthostatic hypotension outliers was previously described under Section 7.1.4 and were also provided as a separate section in the SCS. Refer to section 7.1.4 for reviewer comments and description of results. The sponsor's summary table found in a separate section 2.1.6.5 in the SCS is provided below for the convenience of the regulatory supervisor reading of this review.

The sponsor indicates that 3 ADOs and 3 SAEs of sinus tachycardia or tachycardia were reported, all of which occurred among subjects that received ≤ 3 months of Pal as of the May 31, 2005 cut-off date of these ongoing OL trials (out of 1167 total subjects who received ≤ 3 months of OL drug).

Results of Orthostatic Hypotension Outliers found in a separate Seciton 2.1.6.5 of the SCS

Table 54: Number of Subjects With Treatment-Emergent Orthostatic Hypotension at Anytime During the Open-Label Period
(Pooled Open-label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
Total no. subjects with orthostatic hypotension	3 (3)	7 (5)	6 (3)	23 (5)	3 (3)	8 (6)	12 (3)	38 (5)
Pulse(std-sup) > 15 and DBP(std-sup) < -10	2 (2)	5 (4)	2 (1)	16 (3)	1 (1)	6 (4)	5 (1)	27 (3)
Pulse(std-sup) > 15 and SBP(std-sup) < -20	1 (1)	2 (2)	4 (2)	12 (2)	2 (2)	4 (3)	7 (2)	18 (2)

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 99: Number of Subjects With Abnormal Vitals Sign Values
(Phase 1/2a Studies in Healthy Adult Subjects Who Received PaliperidoneOROS Formulations: Safety Analysis Set)

Parameter Indicator	PALI OROS LOW DOSE[a] (N=154) n (%)	PALI OROS HIGH DOSE[a] (N=200) n (%)	PALI OROS ALL (N=275) n (%)
Standing pulse(bpm)	75	0	75
Increase >=15 and value >=100	43 (57)	0	43 (57)
Supine pulse(bpm)	147	193	268
Decrease >=15 and value <=50	25 (17)	50 (26)	63 (24)
Increase >=15 and value >=100	11 (7)	51 (26)	59 (22)
Standing SBP(mmHg)	75	0	75
Decrease >=20 and value <=90	26 (35)	0	26 (35)
Supine SBP(mmHg)	147	193	268
Decrease >=20 and value <=90	47 (32)	81 (42)	102 (38)
Increase >=20 and value >=180	0	3 (2)	3 (1)
Standing DBP(mmHg)	75	0	75
Decrease >=15 and value <=50	22 (29)	0	22 (29)
Increase >=15 and value >=105	2 (3)	0	2 (3)
Supine DBP(mmHg)	147	193	268
Decrease >=15 and value <=50	67 (46)	141 (73)	163 (61)
Increase >=15 and value >=105	0	3 (2)	3 (1)

Note: Percentages calculated with the number of subjects per parameter as denominator.
[a] Low dose = 3 to 6 mg, and high dose = 9 to 15 mg doses (Section 1.1.3.3.1).

Table 97: Number of Subjects With Treatment-Emergent Orthostatic Hypotension (Phase 1/2a Studies in Healthy Adult Subjects Who Received Paliperidone OROS Formulations: Safety Analysis Set)

	PALI OROS LOW DOSE[a] (N=55) n (%)	PALI OROS HIGH DOSE[a] (N=1) n (%)	PALI OROS ALL (N=56) n (%)
No. subjects with orthostatic hypotension	22 (40)	0	22 (39)
Pulse(std-sup)>15 and sbp(std-sup)<-20	11 (20)	0	11 (20)
Pulse(std-sup)>15 and dbp(std-sup)<-10	18 (33)	0	18 (32)

Note: Percentages calculated with the number of subjects in each group as denominator.
[a] Low dose = 3 to 6 mg, and high dose = 9 to 12 mg doses (Section 1.1.3.3.1).

Table 100: Number of Subjects With Abnormal Vital Signs (Phase 1/2a Studies in Healthy Adult Subjects Who Did Not Receive ER OROS Paliperidone: Safety Analysis Set)

Parameter Indicator	PLACEBO (N=63) n (%)	PALI IR (N=174) n (%)	PALI OTHER (N=155) n (%)	PALI ALL (N=206) n (%)	RISPERIDONE (N=37) n (%)
Standing pulse(bpm)	53	164	151	194	28
Decrease >=15 and value <=50	5 (9)	7 (4)	13 (9)	19 (10)	1 (4)
Increase >=15 and value >=100	10 (19)	114 (70)	129 (85)	150 (77)	22 (79)
Supine pulse(bpm)	63	173	154	205	37
Decrease >=15 and value <=50	8 (13)	13 (8)	23 (15)	28 (14)	7 (19)
Increase >=15 and value >=100	1 (2)	9 (5)	13 (8)	17 (8)	3 (8)
Standing SBP(mmHg)	62	174	152	204	36
Decrease >=20 and value <=90	22 (35)	93 (53)	103 (68)	129 (63)	22 (61)
Increase >=20 and value >=180	0	1 (1)	2 (1)	3 (1)	0
Supine SBP(mmHg)	63	174	155	206	37
Decrease >=20 and value <=90	3 (5)	33 (19)	47 (30)	61 (30)	11 (30)
Standing DBP(mmHg)	62	174	152	204	36
Decrease >=15 and value <=50	10 (16)	83 (48)	98 (64)	123 (60)	14 (39)
Increase >=15 and value >=105	0	9 (5)	21 (14)	29 (14)	1 (3)
Supine DBP(mmHg)	63	174	155	206	37
Decrease >=15 and value <=50	7 (11)	44 (25)	56 (36)	66 (32)	7 (19)
Increase >=15 and value >=105	1 (2)	0	0	0	0

Note: Percentages calculated with the number of subjects per parameter as denominator. See Section 1.1.3.3.1 for a description of the treatment groups.

Table 98: Number of Subjects With Treatment-Emergent Orthostatic Hypotension (Phase 1/2a Studies in Healthy Adult Subjects Who Did Not Receive PaliperidoneOROS Formulations: Safety Analysis Set)

	PLACEBO (N=62) n (%)	PALI IR (N=174) n (%)	PALI OTHER (N=152) n (%)	PALI ALL (N=204) n (%)	RISPERIDONE (N=36) n (%)
No. subjects with orthostatic hypotension	11 (18)	87 (50)	107 (70)	133 (65)	18 (50)
Pulse(std-sup)>15 and sbp(std-sup)<-20	6 (10)	57 (33)	82 (54)	103 (50)	12 (33)
Pulse(std-sup)>15 and dbp(std-sup)<-10	9 (15)	71 (41)	85 (56)	112 (55)	18 (50)

Note: Percentages calculated with the number of subjects in each group as denominator. See Section 1.1.3.3.1 for a description of treatment groups

Table 106: Number of Subjects With Abnormal Vital Sign Values (Phase 1/2a Studies in Subjects With Schizophrenia)

Parameter Indicator	PALI IR (N=34) n (%)	PALI OROS HIGH DOSE[a] (N=111) n (%)	RISPERIDONE (N=55) n (%)
Standing pulse(bpm)	34	111	55
Decrease >=15 and value <=50	0	1 (1)	0
Increase >=15 and value >=100	24 (71)	95 (86)	52 (95)
Supine pulse(bpm)	34	110	54
Decrease >=15 and value <=50	0	1 (1)	1 (2)
Increase >=15 and value >=100	10 (29)	40 (36)	17 (31)
Standing SBP(mmHg)	34	111	55
Decrease >=20 and value <=90	7 (21)	11 (10)	7 (13)
Increase >=20 and value >=180	1 (3)	2 (2)	2 (4)
Supine SBP(mmHg)	34	110	54
Decrease >=20 and value <=90	2 (6)	6 (5)	1 (2)
Increase >=20 and value >=180	0	1 (1)	1 (2)
Standing DBP(mmHg)	34	111	55
Decrease >=15 and value <=50	3 (9)	7 (6)	4 (7)
Increase >=15 and value >=105	5 (15)	8 (7)	8 (15)
Supine DBP(mmHg)	34	110	54
Decrease >=15 and value <=50	2 (6)	6 (5)	2 (4)
Increase >=15 and value >=105	4 (12)	1 (1)	2 (4)

Note: Percentages calculated with the number of subjects per parameter as denominator. See Section 1.1.3.3.1 for a description of the treatment groups.
[a] High dose = 9 to 15 mg doses

Table 105: Number of Subjects With Treatment-Emergent Orthostatic Hypotension (Phase 1/2a Studies in Subjects With Schizophrenia Safety Analysis Set)

Indicator	PALI IR (N=34) n (%)	PALI OROS HIGH DOSE[a] (N=111) n (%)	RISPERIDONE (N=55) n (%)
No. subjects with orthostatic hypotension	11 (32)	44 (40)	29 (53)
Pulse(std-sup)>15 and sbp(std-sup)<=-20	9 (26)	29 (26)	24 (44)
Pulse(std-sup)>15 and dbp(std-sup)<=-10	9 (26)	32 (29)	18 (33)

Note: Percentages calculated with the number of subjects in each group as denominator. See Section 1.1.3.3.1 for a description of the treatment groups.
[a] High dose = 9 to 15 mg doses

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

A comprehensive description of marked outliers and dropouts could not be found in in-text sections of the SCS. Refer to sections 7.1.1-3 for SAEs and ADOs and Section 7.1.3.3. for some potentially clinically remarkable subjects found by the undersigned reviewer in various sections in the N000 submission or in the 120-Day SUR.

Also see Section 4 of this review regarding concerns (from the undersigned reviewer's perspective) in capturing potentially remarkable subjects.

7.1.8.4 Additional analyses and explorations: Weight and Body Mass Index

7.1.8.4.1 Analyses focused on central tendency

Results from the 3 Non-Elderly Short-Term Phase III Trial Dataset (-303, -304 and -305).
Review Comments. *A dose-dependent Pal group mean change compared to placebo was observed for body weight and body mass index (BMI), as anticipated for this drug class. Results from the SCS from the submission are coped below.*

Table 79: Body Weight and BMI: Change From Baseline to End Point
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo (N=355)	ER OROS PAL 3 mg (N=127)	ER OROS PAL 6 mg (N=235)	ER OROS PAL 9 mg (N=246)	ER OROS PAL 12 mg (N=242)	ER OROS PAL 15 mg (N=113)	Total Paliperidone (N=963)	Olanzapine 10 mg (N=364)
Weight (kg)								
N	323	112	215	235	218	107	887	328
Mean baseline (SD)	78.6 (19.88)	73.8 (20.41)	78.6 (19.85)	72.1 (16.46)	78.5 (21.06)	76.5 (23.41)	76.0 (20.02)	78.0 (22.14)
Mean change (SD)	-0.4 (3.49)	0.6 (2.77)	0.6 (3.18)	1.0 (2.97)	1.1 (3.07)	1.9 (3.63)	1.0 (3.12)	2.0 (3.73)
Mean percent (%) change (SD)	-0.5 (4.75)	1.1 (4.02)	0.9 (4.08)	1.5 (4.14)	1.6 (4.01)	2.6 (4.73)	1.5 (4.18)	2.9 (5.02)
Body mass index (kg/m2)								
N	323	112	215	235	218	107	887	326
Mean baseline (SD)	26.9 (6.19)	25.7 (5.86)	27.2 (6.50)	25.0 (5.09)	26.9 (6.30)	26.6 (7.48)	26.3 (6.21)	26.7 (6.98)
Mean change (SD)	-0.2 (1.19)	0.2 (0.95)	0.2 (1.11)	0.4 (1.02)	0.4 (1.03)	0.6 (1.25)	0.3 (1.07)	0.7 (1.24)

Results from Elderly Phase III Trial -302.

Table 81: Body Weight and BMI: Change From Baseline to End Point
(Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)
Weight (kg)		
N	36	73
Mean baseline (SD)	67.2 (9.60)	65.5 (13.14)
Mean change (SD)	-0.0 (2.34)	-0.0 (2.10)
Mean percent (%) (change (SD)	-0.0 (3.23)	-0.0 (3.31)
Body mass index (kg/m2)		
N	36	73
Mean baseline (SD)	25.5 (3.95)	25.1 (5.14)
Mean change (SD)	-0.0 (0.91)	-0.0 (0.84)

Cross-reference: Mod5.3.5.1\R076477-SCH-302\Sec6.5.2

Results from the Open-Label Ongoing Extension Trials (-702, -703, -704, -705).

Table 82: Body Weight and BMI: Change From Baseline to End Point (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali ≤3 months (N=107)	Pla/Pali >3 months (N=128)	Pali/Pali ≤3 months (N=178)	Pali/Pali >3 months (N=505)	Olan/Pali ≤3 months (N=106)	Olan/Pali >3 months (N=143)	Total Pali ≤3 months (N=391)	Total Pali >3 months (N=776)
Weight (kg)								
N	44	21	76	111	56	26	176	158
Mean baseline (SD)	79.9 (21.56)	71.2 (20.85)	77.9 (22.11)	77.3 (24.67)	82.5 (23.14)	77.6 (21.86)	79.9 (22.27)	76.6 (23.71)
Mean change (SD)	0.4 (4.98)	1.4 (9.73)	1.4 (3.90)	2.9 (6.50)	1.6 (4.41)	1.4 (7.79)	1.2 (4.35)	2.5 (7.20)
Mean percent (%) change (SD)	0.6 (6.23)	3.4 (13.46)	1.8 (5.02)	4.1 (8.73)	2.6 (6.46)	1.8 (8.75)	1.8 (5.84)	3.6 (9.45)
Body mass index (kg/m2)								
N	44	21	76	111	56	26	176	158
Mean baseline (SD)	27.7 (6.97)	24.9 (5.64)	26.8 (6.88)	26.7 (7.58)	27.6 (6.65)	26.4 (7.02)	27.3 (6.81)	26.4 (7.25)
Mean change (SD)	0.2 (1.76)	0.6 (3.39)	0.5 (1.31)	1.0 (2.31)	0.5 (1.48)	0.5 (2.42)	0.4 (1.49)	0.9 (2.49)

Note: Results are changes from double-blind baseline to end point (i.e., last evaluation on or before the 31 May 2005 cut-off date).

7.1.8.4.2 Analyses focused on outliers or shifts from normal to abnormal

Results from the 3 Non-Elderly Short-Term Phase III Trial Dataset (-303, -304 and -305).

Table 80: Number of Subjects With Abnormal Weight Values at End Point (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
Weight classification	323	112	215	235	218	107	887	328
Decrease ≥ 7%	22 (7)	2 (2)	6 (3)	6 (3)	3 (1)	2 (2)	19 (2)	3 (1)
Increase ≥ 7%	15 (5)	8 (7)	13 (6)	21 (9)	20 (9)	19 (18)	81 (9)	60 (18)

Note: Percentages calculated with the number of subjects per parameter as denominator.

Reviewer Comments.
Results show dose-dependent effects of Pal on weight gain.

The sponsor notes the following geographical region differences on the magnitude of weight gain effects:
"ER OROS paliperidone-treated subjects, the percentages of subjects with of the weight and BMI increases of ≥7% from baseline to end point also were higher in subjects from North America or Western Europe, who also had higher baseline body weight and BMI, compared to subjects from Eastern Europe or other regions."

Results from the Elderly Phase III Study -302.

Only 1 placebo subject in Study -302 met outlier criteria for increased weight (an increase exceeding 7% from baseline to endpoint, as predefined).

Results from the Open-Label Ongoing Extension Trials (-702, -703, -704, -705).
Reviewer Comments. *As expected weight gain appears to be greater over time during OL Pal treatment as shown below. Yet the extent of Pal induced effects over time is difficult to determine, in the absence of a placebo group (using a DB study design).*

Table 83: Number of Subjects With Abnormal Weight Values at End Point (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
Weight classification	45	21	76	111	56	26	177	158
Decrease ≥ 7%	3 (7)	2 (10)	1 (1)	4 (4)	1 (2)	3 (12)	5 (3)	9 (6)
Increase ≥ 7%	4 (9)	6 (29)	10 (13)	29 (26)	11 (20)	6 (23)	25 (14)	41 (26)

Note: Percentages calculated with the number of subjects per parameter as denominator. Results are based on changes from double-blind baseline to end point (i.e., last evaluation on or before the 31 May 2005 cut-off date).

The sponsor notes the following geographical differences:

"As noted previously, mean body weight and BMI values at baseline were highest for North American subjects, followed by Western European and Eastern European Subjects, and lowest among subjects in other regions. Regional trends in abnormal weight changes from baseline were difficult to interpret due to the small numbers of subjects in some of the region/exposure (≤3 months versus >3 months) groups. For subjects from 3 of the 4 regions (North America, Eastern Europe, and rest of world), higher percentages of subjects who received >3 months versus ≤3 months of ER OROS paliperidone had weight increases of ≥7% from baseline; an opposite trend was observed for Western European subjects."

7.1.9 Electrocardiograms (ECGs)

A Caveat on Group and Time-point Comparisons on a Given Clinical Parameter. *Results of statistical group or time-point comparisons or in-text description of statistical results on clinical parameters could not be found in the SCS. Therefore, group and time-point comparisons described in this review on any given clinical parameter are based on numerical comparisons, unless otherwise specified (results on clinical parameters that were found in the SCS and are described in this review did not include statistical comparisons).*

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

See sections below for ECG results of primarily Phase III trials. See section 7.1.12 for results of a special safety study on QT interval effects. See section 3 of this review regarding a discussion of potential major issues conveyed by reviewers of other disciplines, which includes the Pharmacology Toxicology reviewer who is conducting a review of preclinical information provided in this NDA.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See sections below and Section 7.1 for a description of datasets analyzed and described in this review.

7.1.9.3 Standard analyses and explorations of ECG data

See previous subsections and subsections below.

7.1.9.3.1 Analyses focused on measures of central tendency

Results of Non-Elderly Phase III Short Term Trials (-303, -304 and -305)
Reviewer Comments. *Due to the lengthiness of the 49 page summary table (Appendix 2.7.4.6.2.1.) results are summarized in this review and selected sections of the sponsor's summary tables are shown below.*

The ECG parameter results found in the sponsor's summary table showed results from the following assessment time-points: screening, baseline, and the average value is provided for these 2 pre-dose time-points (referred to as average pre-dose), then 4, 10 and 22 hour post-dose time-points on Days 4 and 8 of DB treatment, in addition to pre-dose, 1-2 hours and 4 hours post-dose time-points on Days 15 and 36, then time-points of Day 29 and Day 43 and a final end-point assessment.

One critical caveat to interpreting vital sign results is that the window of time that could vary across subjects for each scheduled assessment. The following table was copied from the submission (as part of the statistical analysis plan):

Table 1a: Time Intervals for ECG, Lab, Vitals and EPS Scales Visits for R076477-SCH-303, 304, and 305

Variable	Scheduled Visit Number	Time Interval (Label on ouput)	Time Interval (Day)[a]	Target Time Point (Day)
ECG	1,2	Baseline	≤ 1	1
	4	Day 4: 4H pst-ds	2-6[b]	4
	4	Day 4: 10H pst-ds	2-6[b]	4
	4	Day 4: 22H pst-ds	2-6[b]	4
	5	Day 8: 4H pst-ds	7-11[b]	8
	5	Day 8: 10H pst-ds	7-11[b]	8
	5	Day 8: 22H pst-ds	7-11[b]	8
	6	Day 15: pre-ds	12-22	15
	6	Day 15: 1-2H pst-ds	12-22	15
	6	Day 15: 4H pst-ds	12-22	15
	8	Day 29	23-32	29
	9	Day 36: Pre-ds	33-39	36
	9	Day 36: 1-2H pst-ds	33-39	36
	9	Day 36: 4H pst-ds	33-39	36
	10	Day 43	40-end of DB	43

[a] Relative to the first day of double-blind study drug administration
[b] Time point will be assessed based on the scheduled elapsed time (EGPTMNUM) in the data set.
[c] Applicable to all laboratory tests except for prolactin.
[d] Only for prolactin that is assessed at Day 36.

It is not clear how much subjects varied on the timing of a given assessment, but variance across individuals can impact on the interpretation of the results.

Statistical analyses results could not be found in the SCS. Comments below are based on numerical comparisons of the sponsor's results.

I. Time- and Dose-dependent Pal Effects on Increasing Heart Rate

As previously noted, the sponsor's summary tables, as shown later, do not provide results of statistical comparisons and the in-text sections of the SCS generally refer to the appendices for results (to the tables from which data below was obtained). Consequently, reviewer comments are based on numerical comparisons between treatment groups and assessment time-points.

Descriptive statistical ECG results are generally clinically unremarkable except for:

- *Greater group mean increase (from the average pre-dose value) in heart rate that was observed during DB treatment of Pal compared to only small or no mean increases observed in the placebo group.*
- *Group mean increases in heart rate that were observed in the Olanzapine group were intermediate in magnitude compared to that observed in Pal and placebo groups (based on numerical comparisons).*

Since ECG assessments are generally obtained in the supine position, then the ECG results on HR are reflecting changes that are not orthostatic HR changes.

The Pal-induced effect on increasing heart rate appeared to be dose-dependent and time-dependent, as described in the following:

- *The largest treatment-group mean increases consistently occurred at 4 hours post-dose after the first assessment day of DB treatment (which occurred on Day 4 of treatment) in any given Pal group.*
  - *Smaller group mean increases (or little to no change of mean heart rate) were observed on other post-dose time-points of these assessment days (e.g. at 10 or 22 hour post-dose time-points on Days 4, 8, 15) and on other assessment days that did not include a 4-hour post-dose time-point (e.g. Days 29, 36 and 43, based on numerical comparisons of mean changes).*
- *The magnitude of this time-dependent effect appeared to increase with increasing dose-level as follows:*
  - *Group mean increases of approximately 6, 9, 9, 10 and 12 bpm were observed in the 3 mg, 6 mg, 9 mg, 12 mg and 15 mg groups, respectively at 4 hours post-dose on Day 4, compared to a 1.9 mean increase in the placebo group at this time-point on Day 4 (these results are shown in summary tables that follow reviewer comments).*

The 4-hour post-dose time-dependent effect on increased heart rate appeared to attenuate over subsequent DB treatment days that included a 4 hour post-dose time-point (Days 8 and 15) in each Pal group, as follows:

- *Smaller (secondary) peaks appeared to occur at the 4 hour post-dose time-point on subsequent assessment days that included this 4-hour post-dose time-point (which was on Days 8 and 15).*

The placebo group appeared to show a similar but smaller trend for time-dependent mean increase in heart rate as described in the following:

- *Peak mean increases of 1.9 bpm and 1.5 bpm were observed in the placebo group at 4 hours post-dose on Days 4 and 8, respectively, compared to little to no mean changes in heart rate observed on other time-points or other treatment days.*
- *Subsequent assessment days showed small to negligible mean increases as follows: the largest group placebo group mean increase observed on subsequent treatment days was on Treatment Day 29 (time-point not specified) and treatment Day 36 (at the 1-2 hour assessments) in which mean changes were small to negligible (only 1.2 and 0.3 bpm, respectively).*
- *As previously described, the magnitude of mean increases in the placebo group that were observed at 4 hours post-dose time-points on treatment days that included this time-point, were consistently smaller than that observed for Pal groups at these time-points (peak group mean increases as low as 5.8 bpm in the low-dose Pal group and as high as 12 bpm in the high-dose Pal group at the 4 hour post-dose time-point on the first assessment day during DB treatment which was on Day 4, as previously described and as shown in summary tables below).*

The olanzapine group generally showed:

- *A similar time-dependent group mean increase in heart rate that generally peaked at 4 hours post-dose (that attenuated over subsequent days), except for Day 4 in which the 10 hour post-dose assessment showed a slightly greater mean increase in heart rate than observed at the 4-hour post-dose time-point (as shown later).*
- *However, the 4-hour post-dose mean increases of this active control group (on assessment days that included this time-point) are numerically smaller than group mean increases observed in any given Pal group (including the lowest-dose Pal group at the 3 mg dose-level), but were numerically larger than placebo group mean increases in heart rate.*

Potential Dynamic versus Static Drug Effects on the Cardiovascular System

The above observations provide evidence for a dose-dependent and time-dependent drug effect on increasing heart rate. Preliminarily, the results also suggest a drug-effect on heart rate that is more dynamic than static in its effect, whereby drug-induced increases in heart rate may be influenced by underlying non-drug-related changes in heart rate. For example, underlying increases of heart rate (as was observed in the placebo group at 4-hour post-dose time-points) may be exaggerated by Pal treatment. Consequently, one consideration is that greater drug-effects on heart rate may be unmasked by examining drug effects during an appropriate condition in which the cardiovascular system is perturbed. Further investigation is needed to examine this possible dynamic drug effect on heart rate. Refer to the final section of this review for additional comments and recommendations that includes recommendations for cardiovascular challenge studies to unmask a potential dynamic drug effect on the cardiovascular system.

The Data from which Reviewer Comments are Based

The following table shows sections of the sponsor's summary table (Appendix 2.7.4.6.2.1) in which the above-described time-dependent and dose-dependent effects on mean increase in heart rate can be observed.

Selected time-points are highlighted (by the undersigned reviewer) for demonstration purposes (to indicate time-points for peak and secondary peak mean increases, as previously described in this review).

Note that Pal groups (which follow the placebo group) are organized in the order of decreasing (not increasing) dose-level starting with the HD 15 mg group in the table below.

Results of the olanzapine group are shown last.

Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind Phase

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
HEART RATE (beats/min)														
Placebo														
SCREENING	354	76.8	12.92	76.0	47	126								
BASELINE	355	75.1	12.72	75.0	43	114								
AVERAGE PREDOSE	355	76.1	11.52	76.0	48	115								
DAY 4:4H PST-DS	327	77.8	13.53	77.0	38	129	75.9	327	1.9	0.61	11.00	2.7	-25	40
DAY 4:10H PST-DS	323	76.5	13.47	77.0	45	127	75.9	323	0.6	0.66	11.84	1.3	-30	39
DAY 4:22H PST-DS	325	73.9	13.59	73.0	32	120	75.7	325	-1.9	0.58	10.40	-2.0	-29	30
DAY 8:4H PST-DS	315	77.1	13.61	76.0	39	121	75.5	315	1.5	0.72	12.78	0.7	-32	50
DAY 8:10H PST-DS	311	76.3	13.80	76.0	45	124	75.5	311	0.9	0.74	12.98	0.3	-32	49
DAY 8:22H PST-DS	307	73.4	13.59	72.0	43	108	75.5	307	-2.1	0.71	12.51	-2.7	-32	43
DAY 15:PRE-DS	280	72.8	15.12	70.0	36	132	75.2	280	-2.4	0.77	12.92	-3.7	-42	55
DAY 15:1-2H PST-DS	281	75.8	14.82	73.0	40	120	75.2	281	0.5	0.82	13.78	0.0	-41	48
DAY 15:4H PST-DS	279	76.2	14.74	75.0	40	129	75.2	279	0.9	0.82	13.67	1.0	-50	40
DAY 29	206	76.2	14.39	74.5	50	123	74.9	206	1.2	0.99	14.20	0.7	-30	63
DAY 36:PRE-DS	136	73.0	14.52	73.0	47	105	74.7	136	-1.7	1.15	13.44	-2.7	-45	43
DAY 36:1-2H PST-DS	136	74.9	14.30	74.0	48	119	74.7	136	0.3	1.14	13.27	-0.3	-33	44
DAY 36:4H PST-DS	136	74.8	13.81	76.0	45	111	74.6	136	0.2	1.22	14.23	-0.2	-37	41
DAY 43	139	71.7	13.28	69.0	47	103	74.1	139	-2.4	0.98	11.50	-2.7	-32	35
END POINT	350	75.8	14.82	76.0	47	120	76.0	350	-0.2	0.74	13.91	-1.0	-34	63
ER OROS PAL 15 mg														
SCREENING	112	76.9	13.27	76.0	47	117								
BASELINE	113	75.7	12.77	75.0	50	123								
AVERAGE PREDOSE	113	76.6	12.17	76.3	49	118								
DAY 4:4H PST-DS	105	87.6	13.26	88.0	53	122	76.5	105	11.1	1.05	10.79	11.7	-15	48
DAY 4:10H PST-DS	101	84.1	13.98	85.0	51	126	76.6	101	7.5	1.19	11.96	7.0	-40	34
DAY 4:22H PST-DS	105	82.7	14.44	83.0	48	119	76.7	105	6.1	1.15	11.83	4.7	-21	38
DAY 8:4H PST-DS	106	83.1	13.73	85.0	52	116	76.8	106	6.3	1.23	12.64	6.0	-26	36
DAY 8:10H PST-DS	103	81.2	12.50	82.0	53	110	76.6	103	4.5	1.20	12.15	5.5	-37	33
DAY 8:22H PST-DS	105	80.1	14.82	80.0	44	128	76.7	105	3.5	1.33	13.62	1.7	-28	42
DAY 15:PRE-DS	101	77.9	14.84	76.0	49	116	76.8	101	1.1	1.29	12.95	1.3	-39	43
DAY 15:1-2H PST-DS	99	80.5	12.60	82.0	50	109	76.4	99	4.0	1.45	14.46	5.3	-43	39
DAY 15:4H PST-DS	101	83.1	13.72	82.0	52	137	76.9	101	6.2	1.32	13.25	6.7	-26	41
DAY 29	93	76.9	12.76	76.0	50	107	77.2	93	-0.3	1.41	13.58	0.5	-40	34
DAY 36:PRE-DS	76	74.0	11.92	73.0	52	105	77.0	76	-3.0	1.76	15.35	-1.8	-51	32
DAY 36:1-2H PST-DS	80	77.1	13.76	76.0	51	122	77.1	80	-0.0	1.73	15.49	-1.3	-42	53
DAY 36:4H PST-DS	78	77.6	12.64	76.0	52	111	77.0	78	0.7	1.69	14.96	1.7	-37	42
DAY 43	82	73.5	10.78	72.5	51	109	77.0	82	-3.5	1.40	12.69	-5.0	-44	26
END POINT	113	74.8	11.80	73.0	48	109	76.6	113	-1.8	1.20	12.74	-2.3	-44	26
ER OROS PAL 12 mg														
SCREENING	240	78.1	13.70	77.5	50	119								
BASELINE	242	77.0	13.75	77.5	44	149								
AVERAGE PREDOSE	242	77.7	12.63	77.7	46	134								
DAY 4:4H PST-DS	218	88.2	14.49	89.0	43	128	78.0	218	10.2	0.89	13.17	10.7	-28	54
DAY 4:10H PST-DS	211	85.6	14.40	87.0	46	130	77.9	211	7.7	0.89	12.86	7.3	-27	48
DAY 4:22H PST-DS	212	84.0	14.52	84.0	46	120	78.2	212	5.8	0.88	12.86	5.5	-32	48
DAY 8:4H PST-DS	213	85.4	13.54	86.0	47	120	78.0	213	7.4	0.86	12.49	8.0	-29	46
DAY 8:10H PST-DS	207	83.4	14.35	83.0	46	115	78.2	207	5.2	0.90	12.99	4.7	-33	46
DAY 8:22H PST-DS	210	81.5	14.51	82.0	44	123	78.0	210	3.5	0.95	13.73	3.7	-35	48
DAY 15:PRE-DS	198	81.1	14.94	81.0	47	123	78.4	198	2.7	0.89	12.53	3.3	-35	51
DAY 15:1-2H PST-DS	194	83.8	14.81	84.5	40	140	78.4	194	5.4	1.04	14.52	4.8	-52	61
DAY 15:4H PST-DS	194	85.7	16.09	85.0	42	144	78.7	194	7.0	1.19	16.64	5.0	-40	66
DAY 29	174	78.5	15.04	77.0	44	117	78.8	174	-0.3	1.01	13.33	0.3	-51	36
DAY 36:PRE-DS	150	76.9	14.94	75.0	44	138	78.1	150	-1.2	1.01	12.31	-1.2	-30	30
DAY 36:1-2H PST-DS	148	77.9	13.66	77.0	47	109	78.0	148	-0.2	1.05	12.83	1.7	-46	29
DAY 36:4H PST-DS	146	79.4	13.29	79.0	50	114	78.2	146	1.2	1.09	13.13	1.5	-52	32
DAY 43	152	75.8	13.57	74.5	47	112	77.7	152	-1.9	1.05	12.92	-3.0	-52	31
END POINT	238	78.7	14.73	78.0	47	117	77.7	238	1.0	0.89	13.76	0.2	-52	43
ER OROS PAL 9 mg														
SCREENING	243	76.1	12.79	75.0	48	112								
BASELINE	245	75.7	12.71	75.0	42	116								
AVERAGE PREDOSE	245	76.1	11.53	75.3	42	107								
DAY 4:4H PST-DS	234	85.2	14.59	85.0	47	125	76.0	234	9.2	0.80	12.26	8.1	-32	52
DAY 4:10H PST-DS	229	83.1	14.77	82.0	48	126	75.6	229	7.5	0.86	12.94	8.0	-26	55
DAY 4:22H PST-DS	226	80.8	14.43	80.0	46	131	75.8	226	4.9	0.83	12.55	3.3	-26	50
DAY 8:4H PST-DS	221	82.3	13.04	82.0	50	121	75.6	220	6.8	0.79	11.71	6.2	-25	44
DAY 8:10H PST-DS	216	80.0	12.97	80.0	49	135	75.1	215	4.9	0.87	12.76	3.7	-25	48
DAY 8:22H PST-DS	220	78.2	13.37	77.0	46	129	75.5	219	2.7	0.83	12.36	1.3	-24	60
DAY 15:PRE-DS	211	76.0	14.23	75.0	48	123	75.5	210	0.5	0.86	12.44	-0.2	-27	52
DAY 15:1-2H PST-DS	211	79.5	14.34	79.0	46	129	75.6	210	4.0	0.92	13.32	3.8	-29	41
DAY 15:4H PST-DS	210	81.5	13.87	81.0	47	118	75.7	209	5.8	0.84	12.13	5.3	-21	45
DAY 29	188	75.1	14.00	74.0	45	111	74.7	187	0.5	0.82	11.27	0.0	-37	39
DAY 36:PRE-DS	157	72.6	14.32	70.0	43	108	74.6	156	-2.0	1.03	12.85	-2.2	-33	30
DAY 36:1-2H PST-DS	156	74.7	13.91	73.5	46	113	74.6	155	0.1	1.01	12.63	-1.0	-28	38
DAY 36:4H PST-DS	153	75.0	12.39	74.0	47	108	74.2	152	0.8	0.92	11.38	1.7	-31	45
DAY 43	160	72.5	13.20	71.5	44	121	74.7	159	-2.1	0.90	11.30	-1.7	-33	25
END POINT	243	75.7	14.51	74.0	44	121	76.0	242	-0.3	0.79	12.27	-1.2	-33	43

ER OROS PAL 6 mg													
SCREENING	234	76.4	13.75	75.0	51	112							
BASELINE	235	75.4	14.27	77.0	46	122							
AVERAGE PREDOSE	235	75.9	12.63	75.7	51	112							
DAY 4:4H PST-DS	218	85.9	13.68	85.5	53	130	75.9	218	9.9	0.80	11.86	9.8	-20	16
DAY 4:10H PST-DS	209	83.4	14.16	83.0	56	134	76.1	209	7.4	0.87	12.53	7.3	-32	60
DAY 4:22H PST-DS	203	80.4	14.03	79.0	44	118	76.1	203	4.3	0.94	13.33	3.3	-43	52
DAY 8:4H PST-DS	210	83.6	12.92	84.0	52	111	75.9	210	7.7	0.80	11.58	8.0	-22	36
DAY 8:10H PST-DS	201	82.7	12.62	82.0	54	114	75.6	201	7.0	0.86	12.15	8.0	-32	40
DAY 8:22H PST-DS	203	78.9	14.20	78.0	49	117	76.0	203	2.9	0.92	13.10	2.3	-33	38
DAY 15:PRE-DS	187	76.4	14.08	76.0	39	124	75.8	187	0.6	0.88	11.99	1.0	-37	40
DAY 15:1-2H PST-DS	184	79.2	13.72	79.0	44	115	75.6	184	3.6	0.96	13.00	3.7	-44	37
DAY 15:4H PST-DS	176	81.6	13.86	81.0	49	119	75.7	178	5.9	0.99	13.21	4.8	-38	38
DAY 29	157	76.5	13.78	75.0	47	113	75.6	157	0.9	1.03	12.91	0.7	-30	36
DAY 36:PRE-DS	125	74.9	16.54	73.0	47	163	76.2	125	-1.3	1.26	14.14	-2.7	-34	75
DAY 36:1-2H PST-DS	123	75.7	13.85	75.0	44	139	76.0	123	-0.3	1.11	12.28	0.0	-31	51
DAY 36:4H PST-DS	122	77.1	14.04	76.0	39	135	76.1	122	1.1	1.26	13.88	0.0	-36	47
DAY 43	124	75.2	13.69	73.5	47	113	76.1	124	-0.9	1.03	11.47	-1.0	-34	37
END POINT	232	77.8	14.13	77.0	47	118	75.8	232	2.1	0.85	12.94	1.0	-34	37
ER OROS PAL 3 mg														
SCREENING	127	77.3	14.28	76.0	43	132								
BASELINE	127	75.9	14.99	75.0	47	130								
AVERAGE PREDOSE	127	77.0	14.01	76.3	49	125								
DAY 4:4H PST-DS	118	82.6	13.70	81.5	53	120	76.8	118	5.8	1.12	12.17	5.3	-19	38
DAY 4:10H PST-DS	114	81.1	13.79	79.5	49	115	76.9	114	4.1	1.16	12.36	4.7	-27	33
DAY 4:22H PST-DS	118	78.4	14.81	76.0	47	116	76.8	118	1.6	1.27	13.74	1.3	-36	43
DAY 8:4H PST-DS	112	82.4	14.86	82.0	55	130	77.0	112	5.5	1.20	12.66	5.3	-26	56
DAY 8:10H PST-DS	107	80.3	14.28	81.0	52	119	76.9	107	3.5	1.17	14.20	4.3	-28	49
DAY 8:22H PST-DS	113	77.5	13.84	76.0	49	112	76.8	113	0.7	1.20	12.74	2.3	-29	34
DAY 15:PRE-DS	104	75.5	14.30	74.5	52	115	76.5	104	-1.0	1.21	12.35	-1.2	-32	28
DAY 15:1-2H PST-DS	103	79.8	14.66	79.0	53	121	76.5	103	3.4	1.31	13.26	3.3	-38	44
DAY 15:4H PST-DS	104	81.3	15.03	80.0	50	118	76.9	104	4.4	1.36	13.88	4.5	-34	43
DAY 29	96	77.0	14.57	76.0	51	120	77.0	86	-0.0	1.65	15.27	1.0	-40	46
DAY 36:PRE-DS	66	74.8	14.28	73.0	49	109	76.8	66	-2.0	1.63	13.22	-2.8	-34	30
DAY 36:1-2H PST-DS	69	75.3	12.37	73.0	53	109	76.5	69	-1.2	1.67	13.89	0.3	-34	25
DAY 36:4H PST-DS	68	76.8	12.55	77.0	50	102	76.9	68	-0.2	1.63	13.42	2.6	-32	24
DAY 43	70	74.2	13.38	74.0	48	110	76.7	70	-2.5	1.69	14.11	-3.5	-42	34
END POINT	124	76.9	14.24	76.0	48	114	77.2	124	-0.3	1.36	15.11	-0.8	-42	37
Olanzapine 10 mg														
SCREENING	364	77.4	13.50	77.0	45	119								
BASELINE	364	76.0	13.65	74.5	48	117								
AVERAGE PREDOSE	364	76.9	12.14	76.7	47	114								
DAY 4:4H PST-DS	340	79.5	15.07	78.0	46	128	76.9	340	2.6	0.65	12.07	2.3	-33	44
DAY 4:10H PST-DS	330	79.9	15.24	79.0	41	128	76.9	330	2.9	0.72	12.99	2.3	-30	51
DAY 4:22H PST-DS	328	76.2	13.96	75.0	44	115	76.7	328	-0.5	0.65	11.77	-1.0	-32	42
DAY 8:4H PST-DS	332	80.3	13.53	80.0	50	128	77.0	332	3.3	0.73	13.31	3.7	-30	42
DAY 8:10H PST-DS	326	79.9	13.91	80.0	46	120	77.0	326	2.9	0.72	13.06	2.8	-43	51
DAY 8:22H PST-DS	327	76.2	13.16	76.0	43	113	77.0	327	-0.8	0.67	12.03	-1.0	-38	47
DAY 15:PRE-DS	321	76.4	12.96	76.0	46	117	77.0	321	-0.6	0.68	12.12	-1.0	-35	39
DAY 15:1-2H PST-DS	310	80.8	14.44	80.0	48	117	77.1	310	3.8	0.80	14.01	3.2	-36	48
DAY 15:4H PST-DS	307	81.9	14.66	82.0	52	120	77.0	307	4.9	0.80	14.02	3.7	-34	44
DAY 29	262	79.6	13.00	79.0	47	122	77.1	262	2.5	0.82	13.20	2.0	-34	60
DAY 36:PRE-DS	221	75.1	13.29	73.0	50	117	76.7	221	-1.6	0.85	12.61	-2.3	-35	33
DAY 36:1-2H PST-DS	224	76.4	13.46	75.0	43	118	76.7	224	-0.3	0.83	12.37	-0.3	-39	31
DAY 36:4H PST-DS	217	77.9	14.96	77.0	44	129	76.7	217	1.2	0.90	13.31	1.3	-39	43
DAY 43	220	75.2	13.48	74.0	44	113	76.8	220	-1.6	0.85	12.61	-3.2	-33	45
END POINT	357	77.7	13.68	77.0	44	115	76.9	357	0.9	0.69	13.08	-0.7	-33	45

II. Clinically Unremarkable Drug-related Effects on RR

Time and dose dependent effects on mean decreases in RR interval were observed that showed a similar time and dose-dependent pattern (maximal effects appeared to occur at the 4-hour post-dose time-points and increased with increasing dose-level) that was observed for mean increases in heart rate (described above). These observations are likely to be secondary to drug-induced effects on increasing heart rate.

See the results on this parameter below (taken from the sponsor's summary table, Appendix 2.7.4.6.2.1).

Note that selected time-points are highlighted by the undersigned reviewer for demonstration purposes (to denote peak and secondary peak mean decreases, that occurred generally at the

same time-points of pea and secondary peak mean increases observed for heart rate, as previously described in this review).

Also note that Pal groups are shown in order of decreasing dose-level.

Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind Phase (continued)

Analysis Set: Safety

							Base	change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
RR (ms)														
Placebo														
SCREENING	354	803.9	138.95	789.0	476	1277								
BASELINE	355	823.0	143.27	800.0	526	1395								
AVERAGE PREDOSE	355	813.6	128.09	798.7	523	1269								
DAY 4:4H PST-DS	327	795.7	146.11	779.0	465	1579	815.8	327	-20.0	6.73	121.69	-29.3	-452	327
DAY 4:10H PST-DS	323	810.1	149.86	779.0	472	1333	815.6	323	-5.5	7.26	130.39	-13.0	-474	460
DAY 4:22H PST-DS	325	841.2	164.43	822.0	500	1875	817.7	325	23.5	6.88	124.09	17.0	-384	606
DAY 8:4H PST-DS	315	804.0	148.02	789.0	496	1538	819.5	315	-15.5	7.70	136.72	-11.0	-549	404
DAY 8:10H PST-DS	311	813.2	150.09	789.0	484	1333	819.8	311	-7.5	8.04	141.78	-8.7	-536	431
DAY 8:22H PST-DS	307	846.5	158.84	833.0	556	1395	820.6	307	25.9	8.16	143.00	23.3	-539	499
DAY 15:PRE-DS	280	858.5	174.76	857.0	455	1667	823.3	280	35.2	8.94	149.61	36.2	-569	749
DAY 15:1-2H PST-DS	281	822.6	162.93	822.0	500	1500	823.2	281	-0.7	9.32	156.30	-8.0	-490	627
DAY 15:4H PST-DS	279	817.7	162.01	800.0	465	1500	822.5	279	-4.8	9.27	154.85	-16.0	-430	638
DAY 29	206	815.8	152.48	805.5	488	1200	826.7	206	-11.0	10.72	153.88	-10.3	-693	453
DAY 36:PRE-DS	136	855.7	174.56	822.0	571	1277	829.3	136	26.4	13.75	160.33	28.3	-500	520
DAY 36:1-2H PST-DS	136	831.0	163.06	811.0	504	1250	829.8	136	1.2	13.44	156.75	-3.3	-579	486
DAY 36:4H PST-DS	136	831.0	162.12	789.0	541	1333	830.2	136	0.8	14.37	167.62	-3.5	-557	414
DAY 43	139	866.0	161.42	870.0	583	1277	835.3	139	30.7	11.52	135.83	30.3	-320	350
END POINT	350	822.6	165.59	789.0	500	1277	813.9	350	8.7	8.17	152.91	5.0	-693	453
ER OROS PAL 3 mg														
SCREENING	127	803.1	153.69	789.0	455	1395								
BASELINE	127	821.1	159.89	800.0	462	1277								
AVERAGE PREDOSE	127	811.3	147.33	788.3	484	1220								
DAY 4:4H PST-DS	118	746.8	126.80	736.5	500	1132	812.9	118	-66.0	11.01	119.59	-65.3	-396	168
DAY 4:10H PST-DS	114	762.8	136.96	754.5	522	1224	810.8	114	-48.0	12.18	130.02	-55.9	-442	245
DAY 4:22H PST-DS	118	792.7	150.72	789.0	517	1277	812.9	118	-20.2	12.68	137.75	-19.2	-325	353
DAY 8:4H PST-DS	112	750.9	133.00	732.0	462	1091	812.1	112	-61.3	11.65	123.26	-53.8	-378	210
DAY 8:10H PST-DS	107	770.5	137.21	741.0	504	1154	814.0	107	-43.5	13.98	144.66	-45.0	-457	275
DAY 8:22H PST-DS	113	800.1	149.67	799.0	536	1224	813.1	113	-13.0	12.55	133.41	-23.7	-385	383
DAY 15:PRE-DS	104	823.0	152.35	805.5	522	1154	817.0	104	6.0	12.28	125.25	10.0	-285	283
DAY 15:1-2H PST-DS	103	777.5	145.98	769.0	496	1132	817.4	103	-39.9	13.50	137.03	-32.0	-483	281
DAY 15:4H PST-DS	104	764.4	147.20	750.0	508	1200	814.3	104	-49.8	13.61	138.83	-36.3	-432	283
DAY 29	86	808.0	155.56	789.0	500	1176	812.8	86	-4.8	15.60	144.68	-14.7	-442	357
DAY 36:PRE-DS	66	831.6	163.43	822.0	550	1224	811.5	66	20.1	17.09	138.81	22.2	-356	398
DAY 36:1-2H PST-DS	69	817.5	130.47	822.0	550	1132	817.1	69	0.3	17.04	141.54	-4.3	-490	354
DAY 36:4H PST-DS	68	803.8	140.70	779.0	588	1200	811.8	68	-8.1	16.73	137.94	-27.7	-268	412
DAY 43	70	835.8	156.63	811.0	545	1250	813.7	70	22.1	18.46	154.45	29.2	-360	376
END POINT	124	807.6	152.63	789.0	526	1250	809.3	124	-1.7	13.92	154.97	7.0	-376	376
ER OROS PAL 6 mg														
SCREENING	234	810.3	144.46	800.0	536	1176								
BASELINE	235	825.5	161.65	779.0	492	1304								
AVERAGE PREDOSE	235	819.0	138.43	806.3	540	1197								
DAY 4:4H PST-DS	218	717.7	119.65	702.0	462	1132	818.7	218	-100.9	7.98	117.88	-98.8	-438	166
DAY 4:10H PST-DS	209	740.3	127.78	723.0	448	1071	817.1	209	-76.8	8.50	122.93	-69.3	-436	339
DAY 4:22H PST-DS	203	770.3	141.79	759.0	508	1364	816.7	203	-46.5	9.65	137.48	-33.3	-474	434
DAY 8:4H PST-DS	210	735.8	122.57	714.0	541	1154	819.0	210	-83.1	8.22	119.12	-84.2	-395	224
DAY 8:10H PST-DS	201	743.4	117.98	732.0	526	1111	821.4	201	-78.0	8.66	122.84	-86.7	-446	255
DAY 8:22H PST-DS	203	785.7	144.66	769.0	513	1224	817.8	203	-32.1	9.64	137.32	-30.3	-491	381
DAY 15:PRE-DS	187	812.5	153.37	789.0	484	1538	820.0	187	-7.5	9.98	136.45	-17.7	-454	608
DAY 15:1-2H PST-DS	184	781.6	142.62	759.0	522	1364	822.0	184	-40.4	10.65	144.40	-38.2	-421	434
DAY 15:4H PST-DS	178	756.9	132.11	741.0	504	1224	820.3	178	-63.4	10.35	138.15	-53.7	-419	442
DAY 29	157	810.1	147.54	800.0	531	1277	821.4	157	-11.3	11.16	139.86	-14.7	-324	331
DAY 36:PRE-DS	125	834.7	160.92	822.0	368	1277	813.7	125	21.1	11.93	133.37	22.0	-315	368
DAY 36:1-2H PST-DS	123	817.8	147.20	800.0	432	1364	815.4	123	2.4	11.17	123.92	-13.0	-333	434
DAY 36:4H PST-DS	122	803.5	149.09	789.0	444	1538	814.8	122	-11.3	13.62	150.46	-3.3	-319	608
DAY 43	124	825.0	152.31	816.5	531	1277	815.6	124	9.4	11.43	127.26	2.7	-341	368
END POINT	232	796.8	147.65	779.0	508	1277	820.3	232	-23.5	8.98	136.72	-19.7	-341	368

ER OROS PAL 9 mg													
SCREENING	243	811.5	139.42	800.0	536	1250							
BASELINE	245	816.4	144.51	800.0	517	1429							
AVERAGE PREDOSE	245	814.5	133.53	800.7	562	1429							
DAY 4:4H PST-DS	234	726.7	134.00	706.0	480	1277	815.7	234	-89.0	8.00	122.36	-79.2	-543	378
DAY 4:10H PST-DS	229	745.5	136.36	732.0	476	1250	819.4	229	-73.8	8.49	128.55	-75.3	-674	280
DAY 4:22H PST-DS	226	767.6	142.49	750.0	458	1304	816.7	226	-49.1	8.13	122.27	-41.0	-387	318
DAY 8:4H PST-DS	221	747.9	123.79	732.0	496	1200	819.0	220	-71.2	8.20	121.61	-64.8	-525	270
DAY 8:10H PST-DS	216	769.9	125.03	750.0	444	1224	824.4	215	-54.6	9.05	132.71	-43.7	-498	299
DAY 8:22H PST-DS	220	790.1	136.84	779.0	465	1304	819.6	219	-29.9	8.72	129.04	-19.7	-520	302
DAY 15:PRE-DS	211	816.3	149.53	800.0	488	1250	820.6	210	-3.8	9.17	132.94	-4.7	-412	308
DAY 15:1-2H PST-DS	211	779.5	144.41	759.0	469	1304	819.8	210	-40.7	9.64	139.75	-45.3	-559	302
DAY 15:4H PST-DS	210	759.0	136.72	741.0	508	1277	818.8	209	-59.8	9.08	131.28	-60.0	-739	271
DAY 29	188	827.2	159.46	811.0	541	1333	829.3	187	-2.9	8.99	122.96	-7.8	-348	399
DAY 36:PRE-DS	157	857.3	165.01	857.0	556	1395	832.0	156	25.5	12.12	151.41	13.7	-292	421
DAY 36:1-2H PST-DS	156	831.4	158.58	816.5	531	1304	833.4	155	-1.4	11.33	141.08	6.0	-370	307
DAY 36:4H PST-DS	151	822.4	140.00	811.0	556	1277	837.1	152	-14.4	10.30	126.96	-23.3	-502	327
DAY 43	160	853.9	150.40	839.0	496	1364	830.7	159	22.6	10.38	130.90	12.5	-491	428
END POINT	243	821.3	152.58	811.0	496	1364	815.3	242	5.5	8.45	131.49	6.7	-491	428
ER OROS PAL 12 mg														
SCREENING	240	793.0	142.82	774.0	504	1200								
BASELINE	242	804.9	150.29	774.0	403	1364								
AVERAGE PREDOSE	242	799.2	133.83	773.8	453	1320								
DAY 4:4H PST-DS	218	700.3	126.70	674.0	469	1395	796.0	218	-95.6	8.51	125.70	-95.7	-481	349
DAY 4:10H PST-DS	211	722.5	132.38	690.0	462	1304	796.7	211	-74.2	8.68	126.09	-70.7	-413	288
DAY 4:22H PST-DS	212	737.5	136.33	714.0	500	1304	793.9	212	-56.4	8.47	123.39	-53.5	-471	339
DAY 8:4H PST-DS	213	721.7	123.64	698.0	500	1277	796.2	213	-74.5	8.36	122.01	-67.3	-492	261
DAY 8:10H PST-DS	207	742.0	136.36	723.0	522	1304	794.2	207	-52.2	8.81	126.80	-51.3	-440	355
DAY 8:22H PST-DS	210	761.2	147.09	732.0	488	1364	796.0	210	-34.8	9.49	137.59	-32.5	-451	370
DAY 15:PRE-DS	198	766.1	145.46	741.0	488	1277	792.2	198	-26.1	8.44	118.72	-29.0	-446	249
DAY 15:1-2H PST-DS	194	739.8	143.68	710.0	429	1500	791.4	194	-51.6	9.83	136.90	-56.2	-451	454
DAY 15:4H PST-DS	194	726.7	149.32	706.0	417	1429	787.6	194	-60.8	11.04	153.78	-43.0	-481	582
DAY 29	174	794.6	161.75	779.0	513	1364	788.0	174	6.5	10.31	135.97	-9.8	-382	432
DAY 36:PRE-DS	150	809.6	159.18	800.0	435	1364	796.3	150	13.3	10.48	128.35	4.3	-325	324
DAY 36:1-2H PST-DS	148	795.8	148.95	779.0	550	1277	796.9	148	-1.0	10.86	132.17	-18.7	-333	364
DAY 36:4H PST-DS	146	777.8	138.12	759.0	526	1200	794.3	146	-16.4	11.06	133.58	-15.7	-347	353
DAY 43	152	816.8	147.83	805.5	536	1277	798.8	152	18.0	10.22	125.98	25.3	-331	394
END POINT	238	790.2	154.41	769.0	513	1277	799.4	238	-9.2	8.82	136.04	-8.3	-407	471
ER OROS PAL 15 mg														
SCREENING	112	804.9	147.71	789.0	513	1277								
BASELINE	113	814.6	136.35	800.0	488	1200								
AVERAGE PREDOSE	113	810.1	131.32	795.0	511	1238								
DAY 4:4H PST-DS	105	701.2	112.35	682.0	492	1132	810.9	105	-109.7	9.76	100.03	-108.7	-359	142
DAY 4:10H PST-DS	101	734.5	133.43	706.0	476	1176	810.3	101	-75.8	11.49	115.46	-74.0	-389	384
DAY 4:22H PST-DS	105	749.4	144.97	723.0	504	1250	809.9	105	-60.5	11.60	118.86	-50.0	-421	243
DAY 8:4H PST-DS	106	743.8	135.97	706.0	517	1154	807.6	106	-63.8	12.24	125.98	-59.8	-373	310
DAY 8:10H PST-DS	103	758.0	126.96	732.0	545	1132	810.4	103	-52.4	12.26	124.46	-61.3	-421	230
DAY 8:22H PST-DS	105	775.7	151.91	750.0	469	1364	810.1	105	-34.5	12.96	132.81	-26.3	-415	260
DAY 15:PRE-DS	101	798.7	151.61	789.0	517	1224	809.3	101	-10.6	13.18	132.41	-16.3	-412	293
DAY 15:1-2H PST-DS	99	765.9	132.52	732.0	550	1200	812.3	99	-46.4	16.06	159.77	-45.0	-479	317
DAY 15:4H PST-DS	101	741.5	120.81	732.0	438	1154	807.7	101	-66.2	13.27	133.36	-59.7	-410	171
DAY 29	93	802.9	139.27	789.0	561	1200	803.3	93	-0.5	14.65	141.32	-6.0	-368	365
DAY 36:PRE-DS	76	831.5	134.32	822.0	571	1154	804.7	76	26.8	18.68	162.82	9.7	-366	385
DAY 36:1-2H PST-DS	80	802.3	140.14	789.0	492	1176	803.9	80	-1.7	16.75	149.80	-0.2	-380	417
DAY 36:4H PST-DS	78	793.3	129.84	789.0	541	1154	805.8	78	-12.6	16.68	147.34	-25.3	-352	324
DAY 43	82	833.1	118.63	827.5	550	1176	805.4	82	27.7	14.79	133.96	37.3	-313	396
END POINT	113	822.2	131.10	822.0	550	1250	810.1	113	12.1	12.42	132.04	25.3	-313	396
Olanzapine 10 mg														
SCREENING	364	799.5	146.42	779.0	504	1333								
BASELINE	364	815.5	149.07	805.5	513	1250								
AVERAGE PREDOSE	364	807.0	132.72	791.0	529	1271								
DAY 4:4H PST-DS	340	781.7	148.73	769.0	469	1304	807.1	340	-25.1	6.68	123.23	-28.5	-560	309
DAY 4:10H PST-DS	330	779.6	153.73	759.0	469	1463	807.2	330	-27.6	7.66	139.10	-25.7	-513	423
DAY 4:22H PST-DS	328	814.4	153.08	800.0	522	1364	808.9	328	5.5	7.08	128.17	2.9	-428	470
DAY 8:4H PST-DS	332	769.3	133.53	750.0	469	1200	806.1	332	-36.8	7.71	140.49	-36.7	-510	343
DAY 8:10H PST-DS	326	774.5	141.16	750.0	500	1304	806.2	326	-31.7	7.70	139.00	-35.7	-519	432
DAY 8:22H PST-DS	327	812.0	145.62	789.0	531	1395	805.8	327	6.2	7.24	130.96	-0.7	-494	497
DAY 15:PRE-DS	321	807.8	139.16	789.0	513	1304	805.4	321	2.4	7.57	135.60	6.7	-512	412
DAY 15:1-2H PST-DS	310	766.6	139.70	750.0	513	1250	805.3	310	-38.7	8.26	145.45	-32.7	-573	453
DAY 15:4H PST-DS	307	757.3	141.87	732.0	500	1154	805.8	307	-48.5	8.21	143.82	-42.3	-581	415
DAY 29	262	774.4	129.83	759.0	492	1277	804.7	262	-30.4	8.54	138.23	-26.0	-492	327
DAY 36:PRE-DS	221	823.2	143.12	822.0	513	1200	808.2	221	15.0	9.31	138.45	27.0	-442	311
DAY 36:1-2H PST-DS	224	810.1	146.83	800.0	508	1395	808.1	224	2.0	9.08	135.88	-3.2	-418	489
DAY 36:4H PST-DS	217	798.2	153.20	779.0	465	1364	808.7	217	-10.5	9.80	144.35	-17.7	-453	399
DAY 43	220	823.5	148.41	811.0	531	1364	807.7	220	15.8	9.17	136.04	26.8	-421	324
END POINT	357	796.7	145.95	779.0	522	1364	807.1	357	-10.4	7.26	137.24	3.7	-421	362

III. Small to Moderate Dose Dependent QTc Interval Prolongation Effects Near Tmax (at 22 hours-post-dose that generally showed a numerically greater prolongation over treatment days that included a 22-hour post-dose assessment time-point which was on Days 4 and Day 8).

A. QT raw Interval Results.

It is not surprising that QT-raw interval results showed a mean decrease (from the average pre-dose value) during Pal treatment that was similar to the previously described, time-dependent and dose-dependent Pal group mean changes in RR interval (which decreased) and heart rate (which increased). These observations on raw QT interval are likely reflecting a secondary drug effect due to the drug-induced effect on increasing heart rate, given that the QT interval can be influenced by changes in heart. Therefore, the results on raw QT interval are difficult to interpret.

B. QTc Interval Results

Since raw QT interval is dependent on changes in heart rate, the sponsor provided additional QT interval results on corrected QT interval values (QTc) using Fridericia, Bazett's, linear sagie and linear derived methods for correcting raw QT interval values for changes in heart rate.

The following describes the methodology used by the sponsor for calculating each type of QTc interval in their studies:

- Linear Derived: QTcLD (sec) = QT+b[1–RR], where b is the estimated slope using a linear regression techniques as described in Section 3.11.2.1 of the CSR for Study – SCH-1009. This method of QTc is described by the sponsor as a linear model that "incorporates all drug free QT/RR interval data" and is also intended to correct for study specific differences in this data.
- Bazett: $QTcB=QT/RR_{0.5}$
- Sagie: QTlc=QT + 0.154 (1-RR), and
- Fridericia: $QTcF=QT/RR_{(1/3)}$

Calculation of Day Averaged ECG Parameters

The following describes methods for calculating day-averaged QTc parameters (copied from the CSR):

> The primary endpoint was the difference with placebo (Day 1) in day-averaged QTcLD values. Day-averaged parameters were calculated for the 7 days with complete ECG profiles: Days 1 to 4 and 8 to 10. Since times between ECG intervals on a day are unequally spaced, the day-average was calculated as a weighed mean: $\left(\sum_{i=1}^{10}\left(\frac{(V_i+V_{i-1})}{2}*(T_i-T_{i-1})\right)\right)\Big/(T_{10}-T_0)$ with V_i the value (e.g. QTcLD) at time T_i. T_0 being the first assessment on a day (scheduled at 8:00), T_1 being the next (scheduled at 8:30), continuing until the last T_{10} (scheduled at 20:00). Parameters were considered missing, if more than 3 values out of 11 constituting the average are missing. If more than 2 assessments between T_1 (+30min) and T_8 (+4h) were missing, the weighted average was set to missing.

The results on QTc using these various methods are described in the following paragraphs. Summary tables of the data are provided after these reviewer comments.

i) QT-Bazett's Interval Results:

- *The QTc using Bazett's correction revealed clear dose- and time-dependent effects for QT prolongation (which was greater with each increasing dose-level).*
- *While QTcB is generally used for cases when heart rate is low, note that QTcB results show some evidence for dose-dependent QT prolongation at time-points near Tmax (22 hours post-dose).*
- *It is noteworthy that time-points in which QTcB prolongation effects appear to be most prominent is at 22 hours post-dose time-points which is near Tmax, as well as earlier time-points on Day 4 of treatment (Days 4 and 8 were the only days that had both of the 4-hour and 22-hour post-dose time-points).*
- *Given that QTcB is influenced by heart rate and is more appropriately used as a method of correction for low heart rates, the results at least at 4 hour-post-dose time-points may not be reflecting a true QT prolongation effect.*
- *Despite the caveat regarding the significant limitations with using QTcB values to examine potential QT prolongation effects, time-dependent and dose-dependent Pal effects were observed using other methods for determining QTc and a study, described later that was a special safety study on this topic, revealed QT prolongation effects that in part, were dependent on Cmax, at least in a dynamic fashion as discussed later in this review.*

The following are key considerations with interpreting QTc interval effects:

- *A static versus dynamic drug-effect is a key consideration with interpreting the result. One important consideration regarding the influence of heart rate on QT interval results is that drug effects on heart rate as well as on QT interval may be a dynamic effect, rather than a static effect, as previously discussed with respect to heart rate changes and as suggested by the results that were previously shown on heart rate.*
- *QT interval changes are strongly influenced by heart rate.*
- *Given potential dynamic changes in heart rate and in turn, the influence of heart rate changes on QT interval, then the selection of an appropriate QTc interval calculation for any given time-point may also need to be based on dynamic changes (e.g. the rate of change over time) rather than static effects (e.g. the absolute value at a given time-point) which may also vary from one time-point to another (e.g. consider physiological changes over time that may in turn influence the rate of the change of a given ECG parameter).*
- *Despite the caveats to using Bazett's correction method, the time-dependent changes in QTcB interval cannot be ignored and may be reflecting a QT prolongation effect.*
- *Yet, QTcB interval results are likely to be an exaggerated representation of a real drug effect since heart rate is generally not abnormally low in Pal treated subjects.*

Summary Tables with the Sponsor's QTcB Interval Results
The QTcB interval results described above, are shown below and are taken from the sponsor's appendix summary table (as above).

Selected time-points in the data shown below were highlighted or underlined by the undersigned reviewer for demonstration purposes as follows:

- *Yellow highlighting (denoting the 22 hour post-dose time-point),*
- *Green underlining (denoting 4 hour post-dose time-points) and*
- *Other highlighted time-points denote additional time-points where QTc appears to have increased.*

It is important to note when comparing the 12 and 15 mg Pal groups that in the first week of treatment the 15 mg group received 12 mg daily.

Since only selected groups are shown a dose-dependent effect is not clear from the tables below. However, QTc results using other methods are shown later that include results from several Pal groups at different dose-levels that show evidence for a dose-dependent effects (e.g. see QTcF results that are shown later).

Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind Phase (continued)

Analysis Set: Safety

							Base	change from average predose						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
QTC INTERVAL BAZETT (ms)														
QTC INTERVAL BAZETT (ms)														
Placebo														
SCREENING	353	408.4	23.13	408.0	339	481								
BASELINE	355	406.2	22.58	406.0	342	468								
AVERAGE PREDOSE	355	408.2	20.53	406.3	339	460								
DAY 4:4H PST-DS	327	407.8	20.99	407.0	353	488	408.5	327	-0.8	0.87	15.79	-1.3	-42	53
DAY 4:10H PST-DS	322	406.2	21.91	406.5	341	471	408.6	322	-2.4	1.00	17.87	-1.7	-61	74
DAY 4:22H PST-DS	323	406.6	23.36	408.0	333	472	408.6	323	-1.9	0.92	16.61	-3.0	-64	48
DAY 8:4H PST-DS	315	406.1	22.16	407.0	335	463	408.0	315	-1.8	1.00	17.67	-1.0	-62	62
DAY 8:10H PST-DS	311	406.2	22.06	405.0	340	468	407.9	311	-1.7	1.05	18.54	-3.3	-49	70
DAY 8:22H PST-DS	307	407.0	23.72	407.0	342	469	407.7	307	-0.7	1.06	18.64	-1.3	-63	75
DAY 15:PRE-DS	278	405.3	23.66	407.0	336	488	407.8	278	-2.5	1.10	18.38	-2.0	-56	55
DAY 15:1-2H PST-DS	280	404.0	23.25	403.0	344	492	407.8	280	-3.7	1.10	18.42	-3.3	-54	68
DAY 15:4H PST-DS	278	405.8	22.26	407.0	338	481	407.8	278	-2.1	1.10	18.37	0.0	-74	55
DAY 29	205	409.4	24.04	408.0	347	468	408.0	205	1.3	1.34	19.16	0.7	-49	65
DAY 36:PRE-DS	136	407.6	26.03	405.0	345	486	408.2	136	-0.6	1.72	20.10	0.1	-45	58
DAY 36:1-2H PST-DS	134	406.3	24.25	408.0	339	471	408.1	134	-1.8	1.73	20.03	-0.8	-63	73
DAY 36:4H PST-DS	136	405.9	24.73	406.0	347	470	408.0	136	-1.1	1.68	19.61	-0.7	-49	72
DAY 43	139	406.3	22.88	407.0	330	473	406.6	139	-0.3	1.38	16.28	-1.3	-34	51
MAXIMUM VALUE	350	426.4	21.63	427.5	352	492	408.2	350	18.2	0.93	17.32	17.2	-37	75
END POINT	350	408.4	23.32	409.0	330	473	408.2	350	0.2	1.02	19.03	-0.7	-54	65

ER OROS PAL 12 mg														
SCREENING	239	411.1	23.05	409.0	358	480								
BASELINE	241	408.9	23.57	407.0	342	474								
AVERAGE PREDOSE	241	411.9	21.73	410.0	360	472								
DAY 4:4H PST-DS	216	420.2	23.19	418.5	359	505	412.0	216	8.1	1.29	19.00	7.0	-41	119
DAY 4:10H PST-DS	210	418.0	22.08	415.5	363	502	412.3	210	5.7	1.20	17.33	5.7	-52	72
DAY 4:22H PST-DS	209	421.1	21.60	421.0	362	482	412.3	209	8.8	1.27	18.30	9.3	-66	53
DAY 8:4H PST-DS	211	418.2	20.68	418.0	361	476	412.0	211	6.2	1.27	18.41	6.0	-56	70
DAY 8:10H PST-DS	207	417.6	21.33	417.0	370	483	412.2	207	5.4	1.31	18.80	6.0	-56	55
DAY 8:22H PST-DS	209	420.4	21.86	419.0	361	490	412.0	209	8.3	1.26	18.15	8.0	-45	60
DAY 15:PRE-DS	198	416.1	21.93	416.0	357	490	412.9	198	3.1	1.23	17.30	4.3	-53	49
DAY 15:1-2H PST-DS	191	412.1	21.66	410.0	362	463	412.5	191	-0.4	1.35	18.70	0.0	-78	48
DAY 15:4H PST-DS	192	415.9	21.93	416.5	311	468	412.9	192	3.0	1.41	19.80	2.5	-104	63
DAY 29	174	413.5	22.32	414.0	337	467	413.7	174	-0.1	1.35	17.81	1.0	-58	35
DAY 36:PRE-DS	149	414.7	20.40	417.0	342	475	412.8	149	1.9	1.47	17.96	3.0	-46	45
DAY 36:1-2H PST-DS	147	411.2	21.57	413.0	353	476	412.9	147	-1.7	1.61	19.53	-1.7	-60	54
DAY 36:4H PST-DS	144	415.3	21.08	415.0	355	481	413.4	144	1.9	1.46	17.55	2.3	-62	44
DAY 43	150	413.2	21.81	414.0	356	477	413.3	150	-0.1	1.42	17.44	-1.7	-40	55
MAXIMUM VALUE	238	436.6	20.61	435.5	376	505	411.6	238	25.0	1.11	17.10	23.3	-42	118
END POINT	238	413.2	21.17	414.0	356	477	411.6	238	1.5	1.19	18.41	1.0	-45	55
ER OROS PAL 15 mg														
SCREENING	112	411.3	21.21	412.0	359	463								
BASELINE	113	407.5	21.39	409.0	357	459								
AVERAGE PREDOSE	113	410.4	19.40	411.5	359	454								
DAY 4:4H PST-DS	101	417.8	18.41	419.0	364	461	409.4	101	8.4	1.64	16.64	8.5	-31	69
DAY 4:10H PST-DS	100	416.2	21.47	417.5	339	480	410.9	100	5.3	1.95	19.50	5.8	-109	44
DAY 4:22H PST-DS	105	416.9	21.07	419.0	362	474	410.6	105	6.3	1.69	17.28	3.7	-27	52
DAY 8:4H PST-DS	105	415.1	20.07	416.0	360	463	410.4	105	4.7	1.67	17.06	4.0	-30	62
DAY 8:10H PST-DS	103	414.5	19.47	415.0	361	453	410.3	103	4.2	1.94	19.65	3.7	-62	48
DAY 8:22H PST-DS	105	417.1	23.93	417.0	351	479	410.4	105	6.7	2.18	22.34	3.3	-53	92
DAY 15:PRE-DS	100	411.8	22.46	411.0	364	466	410.2	100	1.5	1.95	19.46	1.3	-43	74
DAY 15:1-2H PST-DS	99	411.7	20.25	411.0	363	459	410.1	99	1.6	1.97	19.55	0.5	-41	57
DAY 15:4H PST-DS	100	412.6	20.06	413.5	361	454	410.2	100	2.4	1.86	18.57	4.3	-60	57
DAY 29	93	412.8	19.54	415.0	358	453	410.6	93	2.3	2.08	20.05	3.7	-62	48
DAY 36:PRE-DS	74	411.6	19.19	411.0	371	455	410.6	74	1.0	2.42	20.92	-2.4	-77	44
DAY 36:1-2H PST-DS	79	409.2	19.41	409.0	360	460	411.1	79	-1.8	2.30	20.41	1.0	-85	39
DAY 36:4H PST-DS	77	411.1	19.41	412.0	373	453	410.8	77	0.6	2.44	21.41	-0.5	-65	63
DAY 43	81	410.5	19.89	412.0	360	455	409.8	81	0.7	1.89	17.03	1.0	-46	42
MAXIMUM VALUE	113	433.9	18.49	433.0	384	480	410.4	113	23.5	1.63	17.32	21.7	-17	92
END POINT	113	410.4	20.73	413.0	353	459	410.4	113	0.0	1.62	17.25	1.7	-46	42

The table below shows heart rate changes of the 15 mg group to allow for comparisons with the above QTcB table, since QT interval values can be dependent on heart rate.

Analysis Set: Safety

							Base	change from average predose						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
HEART RATE (beats/min)														
ER OROS PAL 15 mg														
AVERAGE PREDOSE	113	76.6	12.17	76.3	49	118								
DAY 4:4H PST-DS	105	87.6	13.26	88.0	53	122	76.5	105	11.1	1.05	10.79	11.7	-15	48
DAY 4:10H PST-DS	101	84.1	13.98	85.0	51	126	76.6	101	7.5	1.19	11.96	7.0	-40	34
DAY 4:22H PST-DS	105	82.7	14.44	83.0	48	119	76.7	105	6.1	1.15	11.83	4.7	-21	38
DAY 8:4H PST-DS	106	83.1	13.73	85.0	52	116	76.8	106	6.3	1.23	12.64	6.0	-26	36
DAY 8:10H PST-DS	103	81.2	12.50	82.0	53	110	76.6	103	4.5	1.20	12.15	5.5	-37	33
DAY 8:22H PST-DS	105	80.1	14.82	80.0	44	128	76.7	105	3.5	1.33	13.62	1.7	-28	42
DAY 15:PRE-DS	101	77.9	14.84	76.0	49	116	76.8	101	1.1	1.29	12.95	1.3	-39	43
DAY 15:1-2H PST-DS	99	80.5	12.60	82.0	50	109	76.4	99	4.0	1.45	14.46	5.3	-43	39
DAY 15:4H PST-DS	101	83.1	13.72	82.0	52	137	76.9	101	6.2	1.32	13.25	6.7	-26	41
DAY 29	93	76.9	12.76	76.0	50	107	77.2	93	-0.3	1.41	13.58	0.5	-40	34
DAY 36:PRE-DS	76	74.0	11.92	73.0	52	105	77.0	76	-3.0	1.76	15.35	-1.8	-51	32
DAY 36:1-2H PST-DS	80	77.1	13.76	76.0	51	122	77.1	80	-0.0	1.73	15.49	-1.3	-42	53
DAY 36:4H PST-DS	78	77.6	12.64	76.0	52	111	77.0	78	0.7	1.69	14.96	1.7	-37	42
DAY 43	82	73.5	10.78	72.5	51	109	77.0	82	-3.5	1.40	12.69	-5.0	-44	26
END POINT	113	74.8	11.80	73.0	48	109	76.6	113	-1.8	1.20	12.74	-2.3	-44	26

ii. QTc-Fridericia (QTcF) Interval Results. The Fridericia calculation for QTc may be a more appropriate method for calculating QT, since this method is used when heart rate is increased, as was observed with Pal treatment.

As observed with QTcB interval, a dose-dependent and time-dependent effect of Pal appears to exist with QTcF as outlined below:

- *It is notable that the 22 hour post-dose time-points generally revealed the largest mean increases, independent of which method of calculation that was employed (as observed for QTcB and other methods shown later).*
- *Only Days 4 and 8 had the 22 hour post-dose time-point.*
- *Given that 22 hours post-dose is reported by the sponsor as Tmax for Pal (based on Phase I results) this time-point may be reflecting a drug effect on prolonging QT, similar to that observed for QTcB interval.*
- *It is of potential concern that the mean increase at this time-point in greater on Day 8 than Day 4, as shown below, since steady state levels would be expected to be achieved by Day 8.*
- *Additional mean increases can be observed on subsequent treatment days in which the assessment time-point for the given treatment day is not specified or is specified as a pre-dose time-point. The pre-dose time-point would potentially be only within a few hours of Tmax of the preceding dose, given the reported Tmax of 22 hours. Yet, subjects could be discharged after Day 14 from the study. Assessments conducted on days that did not include PK analyses methods (involving multiple and frequent blood sampling over a given study day) were likely to vary across subjects and relative to their dosing. Refer to Seciton 7.1.X for discussion on this potential concern.*
- *The magnitude of the effect on QTc interval appears to be dose-dependent as described in the following. The maximum group mean intervals observed (such as at the post-22 hour post-dose time points), increases across Pal groups of increasing dose-levels (e.g. values of the 3 mg Pal group to the 12 and 15 mg Pal groups, shown in summary tables, below). It is critical to note that the 15 mg group received 12 mg daily during week 1 of treatment (15 mg daily was given thereafter).*

The Potential Role of PK on QT prolongation is likely to exist (at least in part, independent of heart rate changes) due to the following observations:

- *The QTc prolongation effects may be dependent on Cmax levels*
- *Cmax levels may increase over time with multiple dosing and in the presence of a potential accumulation of the drug (e.g. consider potential redistribution of the drug that in turn may either increase plasma levels or increase concentration in the myocardium).*
- *Greater effects may be revealed in conditions that may increase Cmax, such as the following examples:*
  - *Consider potential drug accumulation that may occur with multiple dosing.*
  - *Consider the known food effects of Pal on plasma levels of Pal (in which approximately a 50% increase in plasma levels was observed in the fed compared to fasted states in Phase I food effect studies).*
  - *Other factors that may influence QT interval or Pal drug levels must also be considered (e.g. concomitant medications, among others.*

Theoretically fluctuations in drug levels are at a minimum once steady state is achieved, such that if Cmax levels plays a critical role in QT prolongation effects, then QT prolongation effects

would be attenuated after about 4-5 days of Pal treatment. Yet a degree of fluctuating levels does exist after steady state and can be influenced by other factors, as previously outlined above, as well as be between individual differences.

Refer to the last section of this review for further comment and recommendations.

Summary Tables of QTcF Results

The QTc Fridericia interval results described above are shown below and are taken from Appendix 2.7.4.6.2.1 of the SCS. Some of the results are highlighted by the undersigned reviewer for demonstration purposes.

It is important to note when comparing the 12 and 15 mg Pal groups that in the first week of treatment the 15 mg group received 12 mg daily.

Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind Phase (continued)

Analysis Set: Safety

							Base	change from average predose						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
QTC INTERVAL FRIDERICIA (ms)														
ER OROS PAL 15 mg														
SCREENING	112	395.5	18.39	394.0	357	451								
BASELINE	113	393.0	18.31	391.0	349	445								
AVERAGE PREDOSE	113	395.1	17.35	394.0	356	444								
DAY 4:4H PST-DS	103	393.1	14.96	393.0	350	429	394.2	103	-1.1	1.22	12.36	-0.3	-38	39
DAY 4:10H PST-DS	100	394.5	18.57	393.0	337	465	395.6	100	-1.1	1.48	14.79	-2.0	-74	29
DAY 4:22H PST-DS	105	396.2	18.27	396.0	352	441	395.3	105	0.9	1.31	13.40	1.3	-32	43
DAY 8:4H PST-DS	105	394.2	17.29	394.0	357	439	395.0	105	-0.8	1.20	12.27	-0.3	-33	28
DAY 8:10H PST-DS	103	395.0	17.62	394.0	350	439	395.0	103	-0.0	1.49	15.10	2.3	-47	29
DAY 8:22H PST-DS	105	398.7	20.26	397.0	349	463	395.1	105	3.6	1.62	16.59	1.0	-33	63
DAY 15:PRE-DS	100	395.3	17.58	393.5	357	443	394.9	100	0.4	1.40	14.02	0.0	-29	34
DAY 15:1-2H PST-DS	99	393.0	17.65	391.0	353	436	394.9	99	-1.9	1.36	13.53	-2.5	-42	31
DAY 15:4H PST-DS	100	391.7	17.30	391.0	354	433	394.7	100	-3.0	1.42	14.18	-3.2	-41	31
DAY 29	93	397.0	15.54	395.0	362	435	394.7	93	2.3	1.61	15.55	3.3	-44	45
DAY 36:PRE-DS	74	398.2	14.72	399.0	364	432	394.9	74	3.2	1.78	15.28	3.9	-43	33
DAY 36:1-2H PST-DS	79	393.6	15.78	393.0	350	433	395.5	79	-1.9	1.59	14.12	1.7	-46	24
DAY 36:4H PST-DS	77	394.9	14.28	394.0	372	426	395.2	77	-0.3	1.81	15.91	0.3	-44	37
DAY 43	81	397.6	17.69	397.0	361	441	394.3	81	3.3	1.55	13.99	3.7	-32	43
MAXIMUM VALUE	113	410.9	17.07	410.0	373	465	395.1	113	15.8	1.34	14.29	15.8	-13	63
END POINT	113	396.4	17.52	396.0	354	441	395.1	113	1.2	1.34	14.21	1.7	-33	46
ER OROS PAL 12 mg														
SCREENING	239	394.6	19.49	393.0	353	468								
BASELINE	241	393.4	19.03	393.0	343	455								
AVERAGE PREDOSE	241	395.7	18.16	395.0	352	451								
DAY 4:4H PST-DS	216	395.1	18.17	394.0	346	454	395.6	216	-0.6	0.94	13.78	-0.5	-42	84
DAY 4:10H PST-DS	210	395.1	18.01	394.5	359	467	396.0	210	-0.9	0.94	13.60	-1.8	-70	55
DAY 4:22H PST-DS	209	399.4	17.26	399.0	360	451	395.8	209	3.6	1.01	14.67	4.7	-53	42
DAY 8:4H PST-DS	211	395.3	16.80	395.0	350	460	395.6	211	-0.2	0.97	14.08	0.0	-55	51
DAY 8:10H PST-DS	207	396.4	17.21	395.0	351	458	395.6	207	0.9	0.99	14.29	2.0	-61	43
DAY 8:22H PST-DS	209	400.8	17.60	400.0	355	454	395.7	209	5.1	0.95	13.66	5.3	-42	44
DAY 15:PRE-DS	198	397.0	17.71	397.0	347	445	396.1	198	0.8	0.98	13.85	1.0	-50	36
DAY 15:1-2H PST-DS	191	391.0	17.81	389.0	347	439	395.7	191	-4.8	1.00	13.77	-4.0	-72	24
DAY 15:4H PST-DS	192	393.4	17.70	393.5	332	433	395.8	192	-2.5	1.01	14.06	-1.8	-73	24
DAY 29	174	396.7	17.63	396.0	350	454	396.5	174	0.2	0.95	12.57	0.5	-47	31
DAY 36:PRE-DS	149	399.3	15.80	399.0	353	439	396.4	149	2.8	1.18	14.37	4.0	-33	36
DAY 36:1-2H PST-DS	147	394.8	16.35	393.0	358	440	396.4	147	-1.6	1.21	14.70	-2.0	-38	33
DAY 36:4H PST-DS	144	397.3	16.76	396.0	362	446	396.8	144	0.5	1.14	13.66	1.3	-38	35
DAY 43	150	398.6	17.59	399.0	352	449	397.1	150	1.5	1.02	12.50	1.2	-29	47
MAXIMUM VALUE	238	411.6	17.61	410.5	362	467	395.5	238	16.1	0.89	13.76	16.8	-35	84
END POINT	238	396.2	17.16	395.0	352	449	395.5	238	0.7	0.86	13.24	0.3	-35	47

ER OROS PAL 3 mg														
SCREENING	127	393.4	20.29	393.0	349	458								
BASELINE	127	392.9	19.83	393.0	347	449								
AVERAGE PREDOSE	127	394.3	18.58	394.7	351	453								
DAY 4:4H PST-DS	118	389.9	17.85	388.0	354	441	394.7	118	-4.8	1.10	11.98	-2.5	-40	24
DAY 4:10H PST-DS	113	389.4	18.41	389.0	338	449	395.0	113	-5.6	1.18	12.59	-6.3	-37	25
DAY 4:22H PST-DS	118	395.3	20.73	396.0	339	456	395.0	118	0.4	1.18	12.83	0.3	-29	40
DAY 8:4H PST-DS	112	392.3	19.28	391.5	343	449	394.4	112	-2.2	1.26	13.38	-2.3	-43	35
DAY 8:10H PST-DS	106	391.8	18.43	391.0	350	455	394.7	106	-2.9	1.15	11.83	-3.0	-35	27
DAY 8:22H PST-DS	113	396.0	19.26	395.0	347	458	394.5	113	1.5	1.11	11.81	1.0	-35	39
DAY 15:PRE-DS	104	393.6	19.84	393.0	342	441	394.3	104	-0.7	1.21	12.33	-0.2	-31	36
DAY 15:1-2H PST-DS	103	390.9	17.73	388.0	359	458	394.7	103	-3.8	1.25	12.71	-5.3	-35	39
DAY 15:4H PST-DS	104	391.1	18.53	390.0	352	443	394.6	104	-3.5	1.34	13.65	-4.7	-36	36
DAY 29	86	394.4	18.69	395.5	351	441	394.9	86	-0.5	1.44	13.37	-0.8	-31	33
DAY 36:PRE-DS	66	397.6	18.66	397.5	359	446	398.1	66	-0.5	1.39	11.28	-1.2	-27	27
DAY 36:1-2H PST-DS	69	393.5	19.37	391.0	352	457	397.5	69	-4.0	1.41	11.70	-2.0	-30	25
DAY 36:4H PST-DS	67	395.1	18.48	396.0	352	462	396.6	67	-1.5	1.50	12.29	-2.0	-35	25
DAY 43	70	396.4	18.45	397.0	358	440	397.3	70	-0.9	1.72	14.35	-0.2	-41	35
MAXIMUM VALUE	124	406.9	18.78	407.0	359	462	394.4	124	12.5	0.96	10.72	12.3	-14	40
END POINT	124	394.4	19.76	395.0	342	442	394.4	124	0.1	1.30	14.45	0.2	-41	35
Olanzapine 10 mg														
SCREENING	362	393.0	17.26	392.0	352	439								
BASELINE	364	391.2	18.20	392.0	339	438								
AVERAGE PREDOSE	364	393.1	16.31	393.3	348	444								
DAY 4:4H PST-DS	333	390.5	19.24	390.0	339	464	392.9	333	-2.4	0.72	13.18	-3.0	-37	56
DAY 4:10H PST-DS	327	390.6	18.89	391.0	337	442	393.4	327	-2.8	0.73	13.21	-2.3	-52	50
DAY 4:22H PST-DS	321	393.6	18.47	394.0	352	441	392.7	321	0.8	0.67	12.01	0.7	-40	33
DAY 8:4H PST-DS	330	392.0	18.43	393.0	337	454	393.3	330	-1.4	0.69	12.56	-0.7	-37	44
DAY 8:10H PST-DS	324	393.2	19.70	393.5	344	547	393.3	324	-0.1	0.80	14.43	-1.3	-43	121
DAY 8:22H PST-DS	327	395.3	19.71	395.0	331	466	393.2	327	2.0	0.80	14.54	1.3	-52	58
DAY 15:PRE-DS	321	393.9	18.57	395.0	336	456	393.4	321	0.6	0.69	12.28	1.3	-49	43
DAY 15:1-2H PST-DS	308	390.5	18.69	390.0	338	446	393.1	308	-2.6	0.77	13.57	-2.7	-64	30
DAY 15:4H PST-DS	306	391.9	18.46	393.0	335	451	393.2	306	-1.3	0.76	13.34	0.2	-55	38
DAY 29	260	394.9	18.97	396.0	336	443	394.1	260	0.8	0.87	14.05	0.7	-53	40
DAY 36:PRE-DS	219	395.8	18.50	395.0	343	445	393.9	219	1.9	0.90	13.28	1.3	-37	36
DAY 36:1-2H PST-DS	224	395.1	19.02	395.0	350	446	394.1	224	1.0	0.90	13.47	1.0	-45	34
DAY 36:4H PST-DS	215	396.0	18.70	396.0	353	449	394.1	215	1.9	0.93	13.61	2.0	-40	47
DAY 43	219	394.3	19.08	395.0	346	445	394.1	219	0.2	0.93	13.73	0.0	-57	38
MAXIMUM VALUE	357	409.3	20.16	409.0	363	547	393.3	357	16.0	0.71	13.33	14.7	-24	121
END POINT	357	393.4	20.74	392.0	345	543	393.3	357	0.1	0.82	15.42	-0.7	-57	117
Placebo														
SCREENING	353	393.0	19.89	391.0	339	463								
BASELINE	355	392.3	18.44	390.0	347	447								
AVERAGE PREDOSE	355	393.5	17.18	392.3	342	444								
DAY 4:4H PST-DS	327	391.6	17.56	391.0	345	471	394.0	327	-2.3	0.69	12.46	-3.0	-40	48
DAY 4:10H PST-DS	322	391.3	18.52	390.0	341	447	394.0	322	-2.7	0.79	14.16	-2.5	-46	56
DAY 4:22H PST-DS	323	393.9	19.32	394.0	335	450	394.1	323	-0.2	0.76	13.61	0.0	-42	44
DAY 8:4H PST-DS	315	390.6	18.40	389.0	325	450	393.7	315	-3.1	0.75	13.26	-2.7	-41	40
DAY 8:10H PST-DS	311	391.4	18.16	390.0	330	448	393.7	311	-2.3	0.79	13.91	-2.7	-41	45
DAY 8:22H PST-DS	307	394.7	19.54	396.0	337	452	393.5	307	1.2	0.78	13.71	0.7	-47	59
DAY 15:PRE-DS	278	393.8	18.85	394.0	339	472	393.8	278	0.0	0.80	13.28	-0.6	-50	43
DAY 15:1-2H PST-DS	280	389.8	18.39	390.0	335	450	393.8	280	-4.0	0.79	13.21	-3.3	-41	52
DAY 15:4H PST-DS	278	391.1	18.38	391.0	329	457	393.8	278	-2.7	0.78	13.02	-2.2	-42	39
DAY 29	205	394.6	19.55	393.0	345	454	394.3	205	0.3	0.94	13.44	0.3	-46	52
DAY 36:PRE-DS	136	395.8	20.87	394.5	343	457	394.8	136	1.0	1.25	14.60	-2.2	-31	40
DAY 36:1-2H PST-DS	134	392.7	18.59	391.0	339	442	394.8	134	-2.1	1.21	14.04	-4.0	-39	31
DAY 36:4H PST-DS	136	393.3	19.71	393.5	344	446	394.7	136	-1.3	1.20	13.99	-3.0	-37	48
DAY 43	139	395.5	19.89	396.0	332	451	393.7	139	1.8	1.15	13.51	2.3	-32	40
MAXIMUM VALUE	350	407.7	19.25	408.0	334	472	393.5	350	14.2	0.69	12.95	13.7	-29	59
END POINT	350	394.1	19.25	394.0	332	451	393.5	350	0.6	0.78	14.59	0.7	-39	55

Note that the Olanzapine group shows minimal to no effect on QTc intervals.

The dose-equivalency between olanzapine and Pal is not clear such that a direct comparison between these drugs on safety results is difficult to interpret. However, the Olanzapine dose employed was 10 mg daily, which is a recommended dose-level in approved labeling for this drug. The recommended starting dose of Pal in proposed labeling is 6 mg with recommended dose increases of up to 12 mg and the lowest recommended dose is 3 mg.

Note that above mean increases in QTc observed for the 12 mg dose-levels. The 6 mg dose-level which is not shown above, had mean increases in QTcF of 1.0, 1.9 at 22 hours post-dose on Days 4 and 8 and up to a mean increase of 2.9 msec which occurred on Day 36, pre-dose (which

would correspond to approximately 24 hours after previous dose and only 2 hours after the anticipated Tmax which is reported to be 22 hours post-dose).

iii. QTc Linear Derived Results. The sponsor notes that QTc linear derived (QTcLD) mean increases of up to 3.1 in the HD Pal group during treatment (up to 4.4 in the next highest-dose-level; in the 12 mg Pal group) at 22 hours post-dose on Days 4 and 8 (assessment days that included the 22 hour post-dose time-point) which was observed in all Pal groups. It is important to note that the HD (15 mg/day) group received 12 mg daily on Days 1-7 of the short term trials. The 22 hour post-dose time-point coincides with Tmax, according to the sponsor.

Another notable observation is that there is a numerical trend for a greater mean increase in QTc LD on the Day 8 compared to Day 4 (22-hour post-dose) assessments as follows: 0.3 and 1.6 msec in the 3 mg Pal group, 0,8 and 1.6, msec in the 6 mg Pal group, 2.2 and 2.6 msec in the 9 mg Pal group, and 2.7 and 4.4 msec in the 15 mg Pal group, on Days 4 and 8, respectively (at the 22 hour-post-dose assessment). The Day 15, 29, 36 and 43 assessments did not include a 22-hour post-dose assessment and the possibility for between individual variance on the timing of these assessments needs to be considered, among other considerations.

Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind Phase (continued)

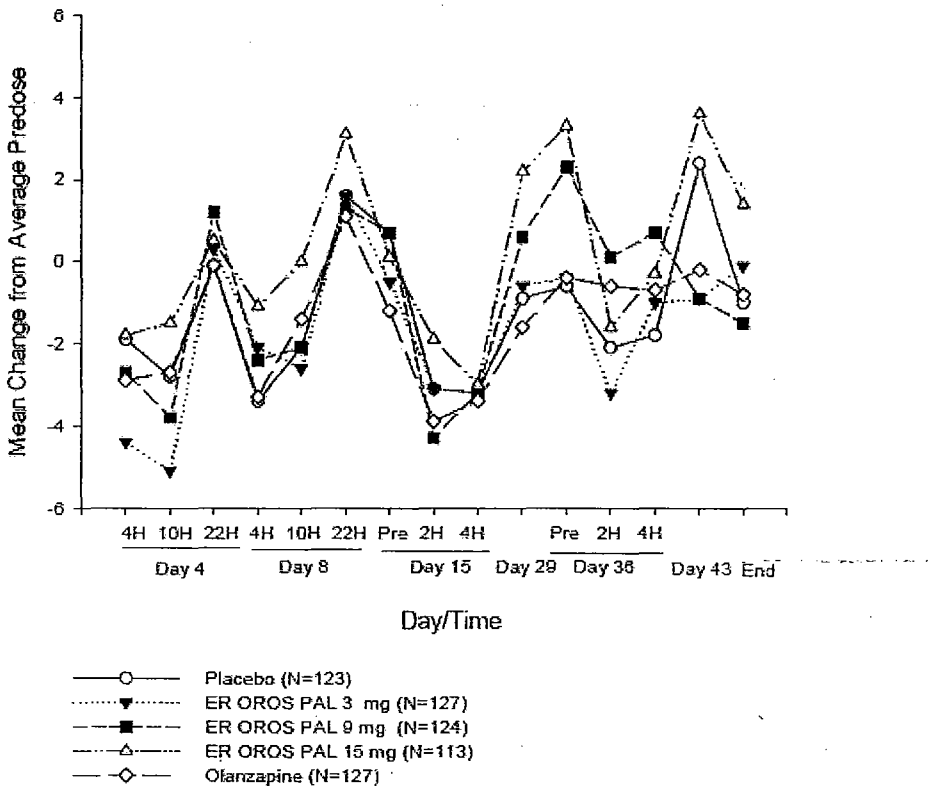
Analysis Set: Safety

							Base	change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
QTC LINEAR DERIVED (ms)														
Placebo														
SCREENING	353	392.8	18.75	391.0	342	458								
BASELINE	355	392.1	17.60	390.0	345	444								
AVERAGE PREDOSE	355	393.1	16.28	392.0	342	440								
DAY 4:4H PST-DS	327	391.4	16.49	391.0	351	466	393.5	327	-2.1	0.66	11.99	-2.0	-36	48
DAY 4:10H PST-DS	322	391.1	17.74	390.0	344	444	393.6	322	-2.5	0.76	13.64	-2.8	-41	54
DAY 4:22H PST-DS	323	393.5	18.73	394.0	332	450	393.7	323	-0.1	0.75	13.43	0.0	-74	40
DAY 8:4H PST-DS	315	390.5	17.55	389.0	330	448	393.3	315	-2.8	0.72	12.71	-2.3	-42	38
DAY 8:10H PST-DS	311	391.2	17.40	390.0	336	447	393.3	311	-2.1	0.75	13.26	-2.7	-38	44
DAY 8:22H PST-DS	307	394.3	18.74	395.0	342	451	393.1	307	1.2	0.75	13.15	0.7	-42	56
DAY 15:PRE-DS	278	393.1	18.69	393.0	336	469	393.3	278	-0.2	0.79	13.20	-0.7	-45	43
DAY 15:1-2H PST-DS	280	389.6	17.32	390.0	341	446	393.4	280	-3.8	0.75	12.52	-3.3	-39	51
DAY 15:4H PST-DS	278	390.8	17.70	391.0	333	455	393.4	278	-2.7	0.75	12.48	-2.3	-40	39
DAY 29	205	394.1	18.46	393.0	350	451	393.9	205	0.2	0.90	12.90	0.3	-43	47
DAY 36:PRE-DS	136	394.9	19.92	394.0	345	454	394.3	136	0.5	1.20	14.04	-1.7	-37	36
DAY 36:1-2H PST-DS	134	392.1	17.91	391.0	340	440	394.3	134	-2.2	1.20	13.84	-3.3	-37	29
DAY 36:4H PST-DS	136	392.8	18.81	392.5	347	445	394.2	136	-1.5	1.18	13.71	-1.8	-37	51
DAY 43	139	395.2	19.36	396.0	332	451	393.4	139	1.7	1.14	13.42	1.5	-30	43
MAXIMUM VALUE	350	406.7	18.26	407.0	341	469	393.1	350	13.6	0.66	12.29	13.0	-25	57
END POINT	350	393.5	18.48	393.0	332	451	393.1	350	0.4	0.75	13.94	0.2	-36	57

ER OROS PAL 15 mg														
SCREENING	112	395.2	17.50	393.5	361	449								
BASELINE	113	393.2	17.38	392.0	352	445								
AVERAGE PREDOSE	113	394.9	16.42	394.3	359	443								
DAY 4:4H PST-DS	103	392.2	13.74	392.0	354	424	394.0	103	-1.8	1.12	11.36	-0.7	-36	33
DAY 4:10H PST-DS	100	393.8	17.45	392.0	337	463	395.3	100	-1.5	1.40	14.03	-2.0	-68	30
DAY 4:22H PST-DS	105	395.6	17.01	394.0	355	441	395.0	105	0.5	1.20	12.31	0.7	-31	33
DAY 8:4H PST-DS	105	393.7	16.19	393.0	360	439	394.7	105	-1.1	1.08	11.08	-0.3	-31	23
DAY 8:10H PST-DS	103	394.8	16.58	394.0	354	438	394.8	103	0.0	1.39	14.07	1.0	-43	27
DAY 8:22H PST-DS	105	397.9	19.33	397.0	350	460	394.9	105	3.1	1.49	15.22	1.0	-27	60
DAY 15:PRE-DS	100	394.8	16.60	393.0	359	443	394.7	100	0.1	1.32	13.19	0.4	-29	31
DAY 15:1-2H PST-DS	99	392.8	16.45	391.0	358	434	394.7	99	-1.9	1.29	12.83	-1.7	-39	27
DAY 15:4H PST-DS	100	391.5	16.23	391.0	358	430	394.5	100	-3.0	1.32	13.20	-3.5	-36	29
DAY 29	93	396.7	15.08	394.0	362	433	394.5	93	2.2	1.53	14.71	2.0	-35	37
DAY 36:PRE-DS	74	398.1	13.76	399.0	368	429	394.8	74	3.3	1.66	14.31	2.3	-35	33
DAY 36:1-2H PST-DS	79	393.7	15.12	394.0	354	433	395.3	79	-1.6	1.52	13.48	2.0	-40	22
DAY 36:4H PST-DS	77	394.7	13.42	393.0	374	426	395.0	77	-0.3	1.71	15.00	0.5	-41	32
DAY 43	81	397.8	16.95	397.0	360	439	394.2	81	3.6	1.48	13.33	3.7	-26	42
MAXIMUM VALUE	113	409.6	16.04	409.0	376	463	394.9	113	14.7	1.26	13.43	14.7	-14	60
END POINT	113	396.4	16.93	396.0	358	439	394.9	113	1.4	1.28	13.63	1.3	-32	43

The following figure illustrates the above described time-dependent pattern of QTcLD taken from the CSR of Study 305. This figure was selected since it comes from one of the placebo controlled, competed Phase III short-term Study 305 which employed the highest Pal dose-level (15 mg/day) and therefore, shows a clear treatment group effect that is dose-dependent with most prominent effects observed at 22 hour post-dose (on Days 4, 8 and 15 which included this post-dose time-point) and at approximately 24 hours post-dose on assessment Days 36 and on Day 43.

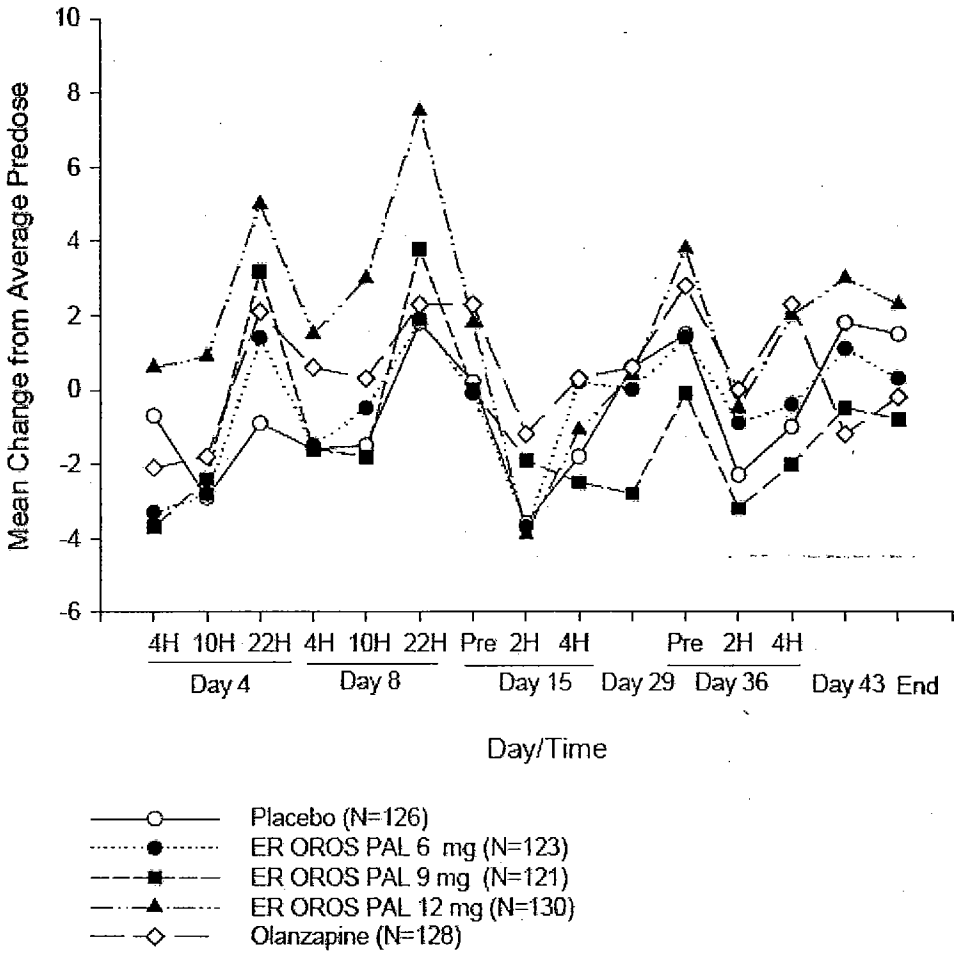
Figure 18: QTcLD Mean Changes From Predose Over Time
(Study R076477-SCH-305: Safety Analysis Set)



Note Fluctuations and Potential Time-dependent Changes in QTc in the Placebo Group
It is noteworthy that the placebo group appears to show fluctuations in mean QTc interval that almost follows a similar time-dependent pattern that was observed for active drug-groups.

The following figure is similar to the above figure, except it is of results from Study 303 which had the next highest dose-level employed in short-term, non-elderly, Phase III trials (as copied from the CSR). Note that the group mean increase in QTcLD group mean increase was greatest in the 12 mg Pal group (7.5 msec maximal group mean increase) compared to placebo (group mean increase of 1.8 msec) that occurred 22 hours post-dose on Day.

Figure 18: QTcLD Mean Changes From Predose Over Time
(Study R076477-SCH-303 Safety Analysis Set)



N is sample size at average predose timepoint
Cross-reference: Attachment 11.1

Note fluctuations in the placebo group that appear to follow to some extent, a similar time-dependent pattern as in the Pal groups.

iv. QTc Interval Values Exceeding 500 msec were Observed but Were Not Generally Consistent with a Drug Effect. The upper end of the treatment group range for QTc interval values (using any method for correction) for any given treatment Pal group exceeded 450 msec on several time-points among various treatment groups. However, this observation did not appear to be drug-related due to the following reasons. The placebo group also showed a maximum value of

450 msec or greater. Furthermore, several treatment groups showed values exceeding 450 msec prior to treatment (at baseline or screening time-points). The results incidence of outliers is discussed in a separate subsection of this review.

IV. Clinically Unremarkable Dose-Dependent Mean Increase in PR Interval

Group mean changes (from the pre-dose average value) on PR interval fluctuated over time in any given treatment group and any observable mean change failed to be of a magnitude to be considered clinically remarkable. However a drug effect on PR appears to exist, as outlined in below that could be reflecting an indirect rather than a direct or primary drug effect on PR:

- *An overall trend for a dose-dependent group mean increase in PR interval appeared to occur and the magnitude of this increase appeared to be greater with each increase in dose-level of Pal and to be more consistently increased over time (more time-points showed a mean increase with each increasing dose-level).*
- *The maximum group mean peak interval in the HD Pal group (15 mg) was 4.3 msec which occurred on Day 8 at 10 hours post-dose with a smaller mean increase observed at this same time-point (10 hours post-dose) on Day 4. These Pal results are compared to mean changes of only 0.5 to -1.9 observed during DB placebo treatment (most time-points had negative values for PR in the placebo group and the maximum placebo group mean increase of 0.5 msec occurred on the same time-point as the peak increase observed in the 15 mg Pal group which was on Day 8 at 10 hours post-dose).*

Summary tables on PR interval Results

The data are shown below (excerpts from Appendix 2.7.4.6.2.1 of the SCS) with highlighting and green underlining of results that were inserted by the undersigned reviewer for demonstration purposes (only the HD Pal and placebo group results are shown). Yellow highlighting denotes the 10 hour-post dose time-points (peak mean increases and secondary peak increases in PR interval in the Pal group).

Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind Phase (continued)

Analysis Set: Safety

							Base	change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max

PR INTERVAL (ms)														
Placebo														
SCREENING	354	152.3	20.95	152.0	88	238								
BASELINE	355	152.6	20.78	152.0	102	250								
AVERAGE PREDOSE	355	152.7	19.79	151.3	97	225								
DAY 4:4H PST-DS	326	153.1	21.78	151.0	110	238	152.7	326	0.4	0.59	10.73	-0.8	-31	65
DAY 4:10H PST-DS	323	152.9	20.64	152.0	104	234	152.5	323	0.3	0.59	10.47	0.3	-42	36
DAY 4:22H PST-DS	324	152.8	21.27	153.0	106	244	152.4	324	0.4	0.61	10.95	1.0	-38	30
DAY 8:4H PST-DS	315	151.8	19.94	150.0	102	227	152.7	315	-0.8	0.62	11.01	0.0	-44	48
DAY 8:10H PST-DS	311	153.4	20.44	152.0	111	209	152.8	311	0.5	0.62	10.95	0.7	-41	31
DAY 8:22H PST-DS	307	151.7	22.07	151.0	100	240	152.7	307	-1.0	0.60	10.49	-1.0	-43	33
DAY 15:PRE-DS	278	152.2	21.83	150.0	106	226	152.9	278	-0.7	0.63	10.58	0.0	-32	34
DAY 15:1-2H PST-DS	281	151.2	20.88	149.0	101	233	153.1	281	-1.9	0.62	10.39	-1.7	-36	29
DAY 15:4H PST-DS	279	151.1	21.17	148.0	104	211	152.9	279	-1.7	0.65	10.79	-1.7	-35	31
DAY 29	206	151.6	21.22	152.0	112	224	153.4	206	-1.9	0.81	11.61	-1.8	-48	30
DAY 36:PRE-DS	136	153.5	17.47	155.5	103	212	153.3	136	0.2	0.82	9.57	0.5	-28	32
DAY 36:1-2H PST-DS	136	151.6	18.71	154.0	104	196	153.4	136	-1.8	0.95	11.06	-1.3	-29	25
DAY 36:4H PST-DS	136	152.2	17.79	151.0	110	205	153.3	136	-1.2	0.91	10.66	0.2	-29	20
DAY 43	139	153.0	20.04	152.0	106	217	154.3	139	-1.3	0.91	10.71	-0.3	-34	36
END POINT	350	150.6	20.74	150.0	102	219	152.7	350	-2.1	0.57	10.67	-2.0	-33	36
ER OROS PAL 15 mg														
SCREENING	112	151.7	21.46	150.0	108	223								
BASELINE	113	152.7	21.69	150.0	109	223								
AVERAGE PREDOSE	113	152.3	21.88	148.3	114	223								
DAY 4:4H PST-DS	105	153.7	21.79	150.0	113	233	152.4	105	1.3	0.99	10.10	1.0	-23	51
DAY 4:10H PST-DS	100	155.4	24.91	150.5	104	250	153.6	100	1.7	1.34	13.43	0.2	-59	75
DAY 4:22H PST-DS	105	153.1	23.36	149.0	110	259	153.1	105	-0.1	1.19	12.19	0.0	-22	83
DAY 8:4H PST-DS	106	153.4	22.20	150.5	110	215	152.7	106	0.8	0.96	9.91	1.0	-32	42
DAY 8:10H PST-DS	103	156.4	24.33	154.0	109	246	152.1	103	4.3	1.16	11.81	3.0	-21	65
DAY 8:22H PST-DS	105	152.8	20.43	150.0	116	218	152.4	105	0.5	1.14	11.68	0.5	-46	36
DAY 15:PRE-DS	101	152.5	21.79	151.0	112	221	151.8	101	0.7	0.95	9.57	1.0	-28	21
DAY 15:1-2H PST-DS	99	152.9	22.21	151.0	110	215	152.3	99	0.6	1.07	10.60	0.5	-37	34
DAY 15:4H PST-DS	100	150.9	21.60	150.0	106	216	151.7	100	-0.7	0.89	8.90	-1.0	-28	20
DAY 29	93	153.5	22.82	153.0	106	212	152.0	93	1.6	1.17	11.33	0.3	-23	40
DAY 36:PRE-DS	75	154.9	24.22	150.0	116	258	153.0	75	2.0	1.24	10.70	2.5	-20	35
DAY 36:1-2H PST-DS	79	154.4	22.51	154.0	114	212	153.7	79	0.7	1.15	10.26	0.0	-24	26
DAY 36:4H PST-DS	78	153.9	25.12	151.5	108	228	153.3	78	0.6	1.24	10.97	-1.0	-25	43
DAY 43	82	154.8	23.08	154.5	110	238	153.2	82	1.6	1.33	12.01	1.3	-34	36
END POINT	113	153.3	22.28	152.0	110	238	152.3	113	1.0	1.08	11.51	0.3	-34	36

V. Overall Conclusion of ECG Results

A clinically significant finding in the above ECG results is a Pal-induced increase in heart rate that is dose and time-dependent. It is possible that greater effects could have been revealed if the study were specifically designed for capturing Tmax and maximal drug effects on heart rate, such as the following consideration. It is critical to consider a potentially dynamic rather than a static drug effect on heart rate (as well as for other clinical parameters) in which the peak heart rate effects occurred at time-points when the placebo group also show increases, while increases in the pal groups were larger.

Despite limitations with the study design of the Phase III trials, it is also notable that various methods for calculation QTc revealed some evidence for dose-dependent effects on prolonging QTc interval near Tmax (which is reported to be at 22 hours post-dose). The largest prolongation effects were observed with QTcB which is not an optimal calculation method for QTc, since Pal generally induced increases in heart rate and heart rate was generally not abnormally low. However, Pal effects on increasing heart rate were not as prominent at the 22 hour post-dose time-points, as observed at other time-points (at the 4 hour post-dose time-points which generally showed the greatest mean increases). Consequently the magnitude of QTcB interval changes may be more accurate at the 22 hour post-dose time-points than at the 4 hour post-dose time-points. The largest group mean increase at the 22 hour post-dose time-point was 8.8 on the first assessment day during treatment (on Day 4) in the 12 mg Pal group (6.2 mean increase was observed in the 15 mg Pal group at 22 hours post-dose on Day 4, which received

12 mg Pal daily during this first week of treatment). This mean increase compares to a mean change of -1.9 in the placebo group at this time-point on this assessment day. It is important to note that a mean increase in heart rate was observed on Day 4, such that QTcB interval values may be an exaggerate representation of a real drug effects in which the actual drug effects may be smaller than values revealed by the Bazett's method for calculation QTc interval.

Using other approaches in calculating QTc that may be more valid methods for determining Pal effects on QT interval (QTcFridericia and lindear derived or linear sagie approaches) a dose-dependent and time-dependent effect of Pall on prolonging QTc interval was also generally revealed. However, the magnitude of this effect was generally moderate to small. A Pal group mean increase of up to 5.1 msec was revealed on Day 8 near Tmax (at the 22 hour time-point) in the 12 mg group for QTc Fridericia interval and a mean increase of up to 3.1 msec was revealed on this same treatment day and time-point in the 15 mg Pal group for QTc linear-derived interval (note that the 15 mg group received 12 mg over the first 7 days of treatment). Figures of QTcLD results in Study -303 showed peak mean increases of up to approximately 7.5 msec on Day 8 (22 hour-post-dose) in the 12 mg Pal group.

A clinically significant concern is that greater QT interval prolongation effects of Pal may occur under conditions that increase Cmax or increase the risk of QT prolongations. The following are key observation that suggest a Cmax dependent effect on Pal induced QT prolongation. QTc interval prolongation effects appeared to be dose-dependent, were generally greatest at a time-point near Tmax (22 hours post-dose) and generally increased over duration of treatment when assessments were conducted near Tmax (Day 8 generally showed greater mean increases than Day 4 near Tmax, which were the only 2 days that had this assessment time-point). As previously discussed it is important to consider the known prominent food effects on plasma Pal levels, the potential for drug accumulation with multiple dosing and other factors that may increase Cmax or factors that may increase risk of QT interval prolongation (e.g. consider concomitant medications).

Pal effects of decreasing RR were generally observed that appear to be secondary to Pal effects on heart rate. The observations on RR do not appear to be clinically remarkable.

Dose-dependent effects of Pal treatment on prolonging PR appear to exist, but the magnitude of the Pal group mean increases in PR were not clinically remarkable.

Results of Elderly Phase III Trial -302

Reviewer Comments. *The descriptive statistical ECG results from Study -302 failed to reveal any new or clinically remarkable findings that were not previously described in this review for the non-elderly, short-term trial dataset (in the previous subsection of this review). Pal group mean increases (from the average pre-dose value) in heart rate were observed during treatment, as shown below (selected sections from Attachment 11.1 of the CSR for this study).*

Study R076477-SCH-302

Output DECG01A: ECG: Means and Mean Changes from Pre-treatment over Time

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	change from average predose Mean	SE	SD	Med	Min	Max
HEART RATE (beats/min)														
Placebo														
SCREENING	37	73.1	13.10	69.0	50	103								
BASELINE	38	72.2	11.57	72.0	50	99								
AVERAGE PREDOSE	38	72.5	11.23	72.2	51	93								
DAY 4:4H PST-DS	35	71.4	11.85	69.0	51	102	72.9	35	-1.5	1.69	10.01	-1.3	-25	17
DAY 4:10H PST-DS	36	69.3	13.16	65.5	47	98	72.5	36	-3.3	2.02	12.14	-0.7	-28	29
DAY 4:22H PST-DS	36	66.3	10.82	63.0	48	100	72.5	36	-6.2	1.52	9.14	-6.5	-27	11
DAY 8:4H PST-DS	35	69.5	11.78	68.0	47	93	72.6	35	-3.0	2.18	12.91	-3.0	-37	27
DAY 8:10H PST-DS	35	68.5	9.56	67.0	54	89	72.6	35	-4.1	2.10	12.40	-2.0	-30	17
DAY 8:22H PST-DS	34	66.2	8.82	67.5	50	87	72.7	34	-6.5	1.81	10.58	-5.2	-29	13
DAY 15	33	68.1	11.41	68.0	49	97	73.1	33	-5.0	1.90	10.89	-3.7	-30	11
DAY 29	31	71.1	12.72	67.0	51	105	72.3	31	-1.2	2.45	13.65	0.3	-28	42
DAY 43	25	68.9	12.62	67.0	49	96	71.3	25	-2.4	2.54	12.68	-1.3	-34	21
END POINT	37	69.5	12.28	68.0	49	96	72.5	37	-3.1	2.14	13.04	-1.3	-34	21
ER OROS PAL														
SCREENING	76	76.5	13.53	78.0	50	103								
BASELINE	76	72.5	14.58	71.5	42	105								
AVERAGE PREDOSE	76	74.7	12.10	75.5	51	100								
DAY 4:4H PST-DS	74	78.1	14.56	78.0	48	128	74.5	74	3.5	1.14	9.79	3.8	-25	33
DAY 4:10H PST-DS	72	78.3	12.92	76.5	50	113	75.0	72	3.3	1.33	11.31	3.2	-27	42
DAY 4:22H PST-DS	72	77.3	14.85	75.5	47	120	74.9	72	2.5	1.20	10.22	1.3	-21	25
DAY 8:4H PST-DS	72	77.9	14.28	77.0	50	123	74.4	72	3.5	1.39	11.83	2.5	-26	36
DAY 8:10H PST-DS	70	78.3	15.04	78.0	49	123	74.2	70	4.1	1.47	12.29	3.2	-29	41
DAY 8:22H PST-DS	72	77.6	18.56	75.0	45	150	74.7	72	2.9	1.64	13.94	0.8	-23	51
DAY 15	72	75.2	15.64	74.0	46	114	74.4	72	0.8	1.42	12.07	1.3	-33	24
DAY 29	68	75.3	16.52	73.5	48	156	74.6	68	0.8	1.62	13.32	0.2	-31	57
DAY 43	64	71.1	10.19	69.0	51	102	74.5	64	-3.4	1.29	10.33	-3.2	-27	16
END POINT	76	72.7	11.91	70.0	51	116	74.7	76	-2.1	1.28	11.18	-1.8	-27	32

The following shows results on RR results (taken from Attachment 11.1 of the CSR)

Study R076477-SCH-302

Output DECG01A: ECG: Means and Mean Changes from Pre-treatment over Time (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	change from average predose Mean	SE	SD	Med	Min	Max
RR (ms)														
Placebo														
SCREENING	37	846.7	148.36	870.0	583	1200								
BASELINE	38	854.1	146.17	833.5	674	1200								
AVERAGE PREDOSE	38	852.2	135.54	839.0	647	1170								
DAY 4:4H PST-DS	35	861.6	134.14	870.0	588	1176	846.7	35	14.9	20.73	122.65	14.0	-232	281
DAY 4:10H PST-DS	36	895.5	160.59	916.0	612	1277	851.7	36	43.7	24.93	149.55	7.0	-296	331
DAY 4:22H PST-DS	36	927.3	145.14	952.0	600	1250	851.7	36	75.5	19.49	116.93	73.2	-153	331
DAY 8:4H PST-DS	35	887.3	151.74	882.0	645	1277	851.9	35	35.3	27.28	161.42	31.7	-293	462
DAY 8:10H PST-DS	35	892.7	120.54	896.0	674	1111	851.9	35	40.7	25.33	149.86	25.3	-230	392
DAY 8:22H PST-DS	34	922.3	125.67	899.0	690	1200	850.6	34	71.7	23.39	136.41	52.8	-173	436
DAY 15	33	903.9	143.35	882.0	619	1224	846.4	33	57.5	22.80	130.95	35.0	-135	372
DAY 29	31	868.1	144.78	896.0	571	1176	855.4	31	12.7	26.12	145.44	-11.0	-377	300
DAY 43	25	898.5	156.49	896.0	625	1224	869.8	25	28.7	30.22	151.11	24.7	-232	403
END POINT	37	888.7	149.95	882.0	625	1224	851.5	37	37.2	25.65	156.05	12.7	-232	403
ER OROS PAL														
SCREENING	76	810.1	148.77	769.0	583	1200								
BASELINE	76	862.6	180.70	839.0	571	1429								
AVERAGE PREDOSE	76	831.2	141.24	804.2	600	1176								
DAY 4:4H PST-DS	74	795.2	149.12	769.0	469	1250	833.1	74	-37.9	12.13	104.37	-55.3	-324	296
DAY 4:10H PST-DS	72	786.9	129.20	784.0	531	1200	828.8	72	-41.9	13.95	118.38	-43.0	-321	315
DAY 4:22H PST-DS	72	804.5	156.50	794.5	500	1277	829.4	72	-24.9	12.34	104.71	-16.3	-278	195
DAY 8:4H PST-DS	72	795.9	147.14	779.0	488	1200	835.3	72	-39.4	14.95	126.83	-24.5	-349	315
DAY 8:10H PST-DS	70	794.4	152.54	769.0	488	1224	838.5	70	-44.1	15.39	128.76	-42.2	-386	373
DAY 8:22H PST-DS	72	814.1	183.32	800.0	400	1333	832.3	72	-18.2	14.99	127.20	-24.0	-302	303
DAY 15	72	831.9	172.38	811.0	526	1304	835.3	72	-3.4	16.09	136.53	-19.8	-226	462
DAY 29	68	828.3	157.16	816.5	385	1250	834.2	68	-5.9	16.40	135.20	-6.7	-320	373
DAY 43	64	860.9	121.15	870.0	588	1176	835.9	64	25.0	14.44	115.53	32.7	-253	333
END POINT	76	845.7	127.72	857.0	517	1176	831.2	76	14.5	13.24	115.41	12.6	-253	333

The following table shows QT Bazett and QTc-Fridericia Interval results (from Attachment 11.1 of the CSR).

Study R076477-SCH-302

Output DECG01A: ECG: Means and Mean Changes from Pre-treatment over Time (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	change from average predose Mean	SE	SD	Med	Min	Max
QTC INTERVAL BAZETT (ms)														
Placebo														
SCREENING	37	427.7	26.52	423.0	371	496								
BASELINE	38	425.7	21.83	423.5	389	479								
AVERAGE PREDOSE	38	426.5	23.33	427.8	389	488								
DAY 4:4H PST-DS	35	422.5	23.75	418.0	381	485	424.8	35	-2.3	3.32	19.64	-3.0	-39	48
DAY 4:10H PST-DS	36	417.2	21.59	417.0	382	461	425.2	36	-8.0	2.99	17.96	-8.5	-36	47
DAY 4:22H PST-DS	36	420.1	19.81	418.0	384	460	425.2	36	-5.1	2.67	16.02	-5.3	-42	24
DAY 8:4H PST-DS	34	416.0	19.89	418.0	372	447	422.9	34	-7.0	2.70	15.75	-5.2	-34	31
DAY 8:10H PST-DS	35	419.2	19.21	419.0	375	459	424.8	35	-5.6	2.69	15.91	-5.5	-36	31
DAY 8:22H PST-DS	34	421.3	18.08	422.0	385	453	425.4	34	-4.1	2.74	15.98	-2.2	-43	32
DAY 15	33	420.1	19.85	420.0	370	469	426.3	33	-6.2	3.92	22.52	-8.0	-64	41
DAY 29	31	423.0	18.44	428.0	369	460	425.5	31	-2.5	3.58	19.92	-2.3	-53	28
DAY 43	25	418.7	17.78	419.0	384	458	423.6	25	-4.9	3.93	19.14	-4.0	-58	27
MAXIMUM VALUE	37	440.2	19.61	439.0	407	485	426.3	37	13.9	2.60	15.84	12.7	-31	48
END POINT	37	422.8	19.90	423.0	384	479	426.3	37	-3.5	3.23	19.67	1.0	-63	27
ER OROS PAL														
SCREENING	74	432.6	26.27	436.0	381	495								
BASELINE	76	425.3	25.98	428.0	337	505								
AVERAGE PREDOSE	76	429.7	24.17	431.0	375	497								
DAY 4:4H PST-DS	70	425.6	24.85	423.0	379	499	428.4	70	-2.9	1.96	16.44	-1.0	-43	27
DAY 4:10H PST-DS	72	429.3	24.29	429.0	373	498	428.7	72	0.6	2.26	19.17	-0.3	-39	57
DAY 4:22H PST-DS	72	433.0	26.62	432.5	378	529	428.8	72	4.2	2.08	17.67	5.2	-45	39
DAY 8:4H PST-DS	71	427.1	21.80	426.0	369	497	427.3	71	-0.2	2.39	20.18	-0.3	-63	43
DAY 8:10H PST-DS	70	428.6	22.38	426.5	385	490	428.0	70	0.6	2.44	20.43	1.3	-56	44
DAY 8:22H PST-DS	71	429.5	24.09	428.0	372	485	427.4	71	2.1	2.68	22.57	5.7	-99	53
DAY 15	72	427.2	24.39	427.0	380	475	428.0	72	-0.8	2.39	20.26	-0.5	-41	59
DAY 29	67	426.2	24.81	430.0	378	496	428.4	67	-2.1	2.15	17.58	-1.5	-35	45
DAY 43	63	425.6	27.22	424.0	366	506	428.3	63	-2.7	2.71	21.53	-1.0	-74	77
MAXIMUM VALUE	76	450.8	23.58	449.0	405	529	429.7	76	21.1	1.85	16.10	20.3	-14	77
END POINT	76	429.1	28.75	427.0	366	506	429.7	76	-0.6	2.54	22.11	-0.3	-74	77
QTC INTERVAL FRIDERICIA (ms)														
Placebo														
SCREENING	37	415.0	25.46	413.0	367	471								
BASELINE	38	413.8	19.18	415.5	374	452								
AVERAGE PREDOSE	38	414.3	21.42	410.0	366	462								
DAY 4:4H PST-DS	35	411.3	24.03	406.0	371	470	412.2	35	-0.9	2.56	15.12	0.0	-31	39
DAY 4:10H PST-DS	36	408.8	23.12	405.5	362	471	413.0	36	-4.2	2.33	14.00	-4.8	-29	48
DAY 4:22H PST-DS	36	414.3	22.60	412.5	374	459	413.0	36	1.4	2.63	15.81	4.0	-33	39
DAY 8:4H PST-DS	34	406.4	18.77	405.5	367	441	411.1	34	-4.7	2.20	12.81	-3.0	-45	15
DAY 8:10H PST-DS	35	410.7	20.67	411.0	360	464	412.6	35	-1.8	2.00	11.86	-4.0	-29	24
DAY 8:22H PST-DS	34	415.2	16.39	414.5	381	455	413.0	34	2.2	2.07	12.07	2.5	-24	32
DAY 15	33	412.2	19.39	416.0	370	446	413.6	33	-1.3	2.88	16.54	-1.0	-36	29
DAY 29	31	412.3	19.80	412.0	370	455	413.5	31	-1.2	2.75	15.29	0.3	-41	33
DAY 43	25	410.3	19.13	407.0	383	448	412.9	25	-2.5	2.58	12.90	-4.0	-34	30
MAXIMUM VALUE	37	428.8	22.15	426.0	390	471	414.1	37	14.7	2.00	12.17	13.0	-8	48
END POINT	37	413.7	21.75	409.0	382	467	414.1	37	-0.3	2.46	14.95	-2.7	-34	33
ER OROS PAL														
SCREENING	74	416.8	23.40	417.5	370	466								
BASELINE	76	413.6	22.14	412.5	337	480								
AVERAGE PREDOSE	76	415.6	22.55	413.5	360	472								
DAY 4:4H PST-DS	70	409.3	22.09	405.0	373	482	414.9	70	-5.6	1.62	13.59	-6.3	-48	24
DAY 4:10H PST-DS	72	411.7	22.98	408.0	369	476	414.4	72	-2.7	2.11	17.89	-1.5	-45	45
DAY 4:22H PST-DS	72	416.3	24.44	414.0	346	506	414.4	72	1.9	1.92	16.28	2.5	-44	37
DAY 8:4H PST-DS	71	410.4	20.57	409.0	348	470	413.8	71	-3.4	2.07	17.47	0.7	-59	40
DAY 8:10H PST-DS	70	411.3	20.55	412.0	359	462	414.4	70	-3.0	2.14	17.87	-0.3	-52	37
DAY 8:22H PST-DS	71	413.5	22.12	415.0	354	462	413.7	71	-0.2	2.39	20.16	2.0	-81	44
DAY 15	72	413.0	21.73	414.5	363	460	414.1	72	-1.1	1.81	15.39	-1.0	-35	43
DAY 29	67	412.0	24.08	412.0	361	491	414.7	67	-2.6	1.90	15.56	-0.7	-49	45
DAY 43	63	414.5	25.32	415.0	360	502	414.3	63	0.2	2.30	18.28	3.0	-51	69
MAXIMUM VALUE	76	431.8	23.85	431.0	378	506	415.6	76	16.2	1.63	14.21	15.5	-16	69
END POINT	76	416.8	26.69	415.5	360	502	415.6	76	1.2	2.17	18.94	2.8	-51	69

Results of QTcLD are shown below given possible QT prolongation effects noted for the short-term trial dataset.

Study R076477-SCH-302

Output DECG01A: ECG: Means and Mean Changes from Pre-treatment over Time (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	change from average predose Mean	SE	SD	Med	Min	Max

QTC LINEAR DERIVED (ms)														
Placebo														
SCREENING	37	414.2	24.13	412.0	368	464								
BASELINE	38	412.9	17.92	413.0	377	451								
AVERAGE PREDOSE	38	413.4	20.07	409.5	370	455								
DAY 4:4H PST-DS	35	411.0	23.32	405.0	373	469	411.4	35	-0.4	2.56	15.15	1.5	-34	42
DAY 4:10H PST-DS	36	408.6	22.97	405.0	365	472	412.1	36	-3.5	2.40	14.43	-5.3	-32	52
DAY 4:22H PST-DS	36	414.3	21.83	412.0	377	458	412.1	36	2.1	2.61	15.64	3.5	-35	38
DAY 8:4H PST-DS	34	406.1	18.01	405.0	370	440	410.4	34	-4.3	2.14	12.47	-2.2	-43	15
DAY 8:10H PST-DS	35	410.8	20.10	411.0	365	465	411.7	35	-0.9	1.99	11.76	-2.7	-29	24
DAY 8:22H PST-DS	34	414.9	15.83	414.5	384	453	412.1	34	2.8	1.98	11.55	1.8	-20	33
DAY 15	33	411.8	18.47	415.0	370	445	412.7	33	-0.9	2.63	15.08	-0.7	-34	25
DAY 29	31	412.0	19.49	412.0	370	454	412.7	31	-0.7	2.68	14.91	-1.0	-37	37
DAY 43	25	410.0	18.61	405.0	384	447	412.2	25	-2.2	2.44	12.21	-3.7	-28	30
MAXIMUM VALUE	37	428.1	21.68	425.0	392	472	413.2	37	14.9	1.97	11.99	12.7	-8	52
END POINT	37	413.4	21.24	408.0	384	465	413.2	37	0.3	2.37	14.42	-1.3	-28	37
ER OROS PAL														
SCREENING	74	415.3	22.16	416.0	373	465								
BASELINE	76	412.3	21.29	412.0	337	472								
AVERAGE PREDOSE	76	414.3	21.56	411.8	362	465								
DAY 4:4H PST-DS	70	408.1	20.85	405.0	375	478	413.8	70	-5.6	1.55	12.97	-5.5	-47	23
DAY 4:10H PST-DS	72	410.5	21.77	407.0	371	470	413.2	72	-2.7	1.99	16.90	-2.7	-43	42
DAY 4:22H PST-DS	72	414.6	23.24	413.5	351	498	413.1	72	1.4	1.84	15.62	1.3	-43	36
DAY 8:4H PST-DS	71	409.4	19.68	407.0	352	466	412.7	71	-3.3	1.99	16.75	0.3	-57	38
DAY 8:10H PST-DS	70	410.2	19.39	410.0	362	461	413.2	70	-3.0	2.02	16.94	-1.0	-47	35
DAY 8:22H PST-DS	71	411.8	21.59	413.0	358	457	412.6	71	-0.8	2.38	20.09	0.7	-87	43
DAY 15	72	411.6	21.08	413.5	365	460	413.0	72	-1.4	1.75	14.88	-1.7	-35	40
DAY 29	67	411.0	23.24	410.0	363	489	413.5	67	-2.5	1.87	15.33	-0.8	-50	44
DAY 43	63	413.9	24.17	415.0	363	500	413.1	63	0.8	2.17	17.26	3.8	-42	68
MAXIMUM VALUE	76	429.9	22.90	428.0	380	500	414.3	76	15.6	1.57	13.66	14.8	-16	68
END POINT	76	415.8	25.50	415.0	363	500	414.3	76	1.5	2.08	18.15	3.7	-42	68

Results of Ongoing Open-Label Extension Long-Term Trials (-702, -703, -704, -705)

Reviewer Comments. *While noting previously described serious limitations with this longterm dataset the following conclusions can be made from this safety dataset (comments and conclusions are based on group mean numerical comparisons of results provided in Appendix 2.7.4.6.2.2. found in the SCS, results of any statistical analyses could not be found in the SCS).*

Results were generally similar to those observed in the short-term trials and did not reveal any new clinically, remarkable findings that are not already described in this review for the short-term trial dataset.

I. Pal Group Mean Increases in Heart Rate.

The conclusions are generally based on data in which over 50 assessed subjects, which was generally for time-points of up to 24 weeks of OL treatment in the > 3 month subgroups, as previously discussed in this review).

As observed with the short-term trial datasets, group mean increases (from the average pre-dose value) in heart rate were observed during DB or during OL Pal treatment in subjects that previously received DB placebo.

Subjects previously receiving DB Pal showed little to no mean increases in heart rate during OL Pal treatment.

Note that a group mean increase of up to 8.4 bpm was observed at week 1 of OL Pal treatment in the DB-Placebo/OL-Pal ≤ 3month subgroup.

The treatment group that previously received olanzapine (DB) showed group mean increases in heart rate upon being switched to OL Pal treatment in the extension trial that continued for several weeks during OL Pal treatment.

A Caveat. *It is critical to note that a flexible dose design was employed during OL trials, in contrast to the fixed dose design in DB trials. Furthermore, consider potential between subject differences on the actual timing of assessments and on dosing (as previously discussed in Section 7.1.X). See these results below (taken from Appendix 2.7.4.6.2.2). Also as previously noted, some data points have insufficient sample sizes.*

Studies R076477-SCH-702, R076477-SCH-702, R076477-SCH-704, and R076477-SCH-705

Output DSCH01: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Pass Mean	N	change from average predose Mean	SD	SD	Med	Min	Max
HEART RATE (beats/min)														
Pla/Pali <=1 months														
BASELINE (DB)	107	71.6	11.73	73.0	47	102								
AVERAGE PREDOSE	107	74.1	11.39	73.7	51	101								
DAY 4 (DB),4H PST	106	76.2	11.74	74.0	50	106	74.1	106	1.1	1.08	11.06	1.7	-25	37
DAY 4 (DB),10H PST	104	74.6	13.82	73.5	52	116	74.2	104	0.4	1.18	12.03	0.7	-30	37
DAY 4 (DB),22H PST	103	70.9	12.44	70.0	48	100	73.9	102	-3.0	1.07	10.73	-4.0	-27	30
DAY 8 (DB),4H PST	106	74.7	13.45	73.5	47	111	74.2	106	0.5	1.32	12.66	0.0	-37	50
DAY 8 (DB),10H PST	106	76.5	12.87	74.0	52	115	74.2	106	1.3	1.32	12.63	1.4	-22	34
DAY 8 (DB),22H PST	106	71.3	13.13	71.0	45	103	74.2	106	-1.3	1.15	11.87	-1.2	-31	19
DAY 15 (DB)	21	66.2	9.67	67.0	49	83	73.0	21	-6.8	2.31	10.59	-6.0	-30	9
DAY 15 (DB),PRE-DS	85	74.0	14.64	70.0	49	115	74.5	85	-0.5	1.36	12.57	-1.4	-36	30
DAY 15 (DB),1-2H PST	85	77.6	14.42	76.0	50	109	74.6	85	3.1	1.62	14.94	3.7	-34	40
DAY 15 (DB),4H PST	85	76.9	13.84	76.0	42	102	74.5	85	3.4	1.46	13.44	3.5	-26	37
DAY 29 (DB)	85	74.8	13.82	73.0	51	115	74.4	85	0.4	1.39	12.78	1.5	-28	38
DAY 36 (DB),PRE-DS	16	72.7	13.62	70.5	48	101	74.0	16	-1.3	1.98	11.90	-3.2	-26	32
DAY 36 (DB),1-2H PST	18	76.4	11.30	76.5	54	101	73.6	18	3.8	1.81	11.36	3.2	-17	19
DAY 36 (DB),4H PST	16	75.2	13.39	74.0	52	101	73.5	16	1.7	2.06	12.39	1.5	-26	33
DAY 43 (DB)	53	70.5	12.41	68.0	49	103	73.5	52	-1.0	1.66	11.95	-1.1	-34	26
END POINT (DB)	107	76.4	14.37	73.0	49	130	74.1	107	1.3	1.32	13.70	1.0	-34	38
BASE (OPEN)	107	74.3	14.36	73.0	49	130	74.1	107	0.2	1.39	13.38	0.0	-34	38
DAY 4 (OPEN)	97	82.1	16.33	81.0	45	132	74.2	97	7.9	1.68	16.62	8.1	-26	64
WEEK 1 (OPEN)	95	82.6	15.80	81.0	56	112	74.1	95	8.4	1.57	15.36	8.0	-27	38
WEEK 2 (OPEN)	90	80.4	15.11	80.0	54	114	74.7	90	5.7	1.38	13.11	6.2	-30	33
WEEK 4 (OPEN)	74	76.7	14.84	75.5	42	111	74.2	74	2.2	1.44	12.42	-1.0	-22	36
WEEK 8 (OPEN)	36	77.1	15.21	76.0	49	115	76.2	36	0.8	2.31	13.87	0.0	-31	36
WEEK 16 (OPEN)	1	66.0		66.0	66	66	85.7	1	-19.7			-19.7	-20	-20
END POINT (OPEN)	106	76.6	14.63	76.0	42	115	74.1	106	1.4	1.34	12.77	1.2	-31	38
Pla/Pali >1 months														
BASELINE (DB)	128	71.4	12.82	71.5	48	114								
AVERAGE PREDOSE	128	74.7	11.39	75.2	49	109								
DAY 4 (DB),4H PST	125	76.8	14.32	76.0	49	132	75.0	125	1.5	1.02	11.43	1.7	-30	40
DAY 4 (DB),10H PST	125	74.8	13.91	75.0	46	127	74.5	125	0.5	1.04	11.62	-0.1	-26	38
DAY 4 (DB),22H PST	126	72.7	13.65	71.0	47	115	74.7	126	-1.0	0.92	10.41	-2.1	-26	36
DAY 8 (DB),4H PST	127	75.2	13.06	74.0	47	104	74.7	127	0.5	1.10	12.36	0.0	-26	48
DAY 8 (DB),10H PST	126	73.1	13.63	73.0	45	113	74.4	126	-1.4	1.16	13.03	-1.0	-32	49
DAY 8 (DB),22H PST	126	72.3	14.04	71.0	42	108	74.7	126	-2.5	1.18	13.21	-3.0	-31	43
DAY 15 (DB)	9	73.0	15.02	70.0	56	97	71.4	9	1.6	2.78	8.11	4.0	-13	11
DAY 15 (DB),PRE-DS	116	72.2	15.04	69.0	37	114	74.8	116	-2.6	1.16	12.42	-2.6	-22	55
DAY 15 (DB),1-2H PST	117	74.5	14.06	73.0	48	108	74.8	117	-0.4	1.13	12.68	-0.3	-30	41
DAY 15 (DB),4H PST	118	74.8	15.76	73.0	48	138	75.0	118	-0.2	1.32	13.37	-0.5	-30	48
DAY 29 (DB)	106	74.7	14.37	73.0	50	112	73.9	106	0.7	1.40	14.36	0.8	-25	63
DAY 36 (DB),PRE-DS	79	73.1	15.68	74.0	47	106	74.7	79	-1.6	1.64	13.71	-1.7	-31	43
DAY 36 (DB),1-2H PST	78	74.9	15.65	74.5	48	139	74.9	78	-0.0	1.69	14.02	-1.2	-33	44
DAY 36 (DB),4H PST	78	74.1	13.87	76.0	45	111	74.9	78	-0.8	1.62	14.36	-3.2	-37	41
DAY 43 (DB)	88	71.7	14.36	70.0	47	101	74.5	88	-1.8	1.36	11.78	-1.8	-32	35
END POINT (DB)	128	73.0	14.86	73.5	47	113	74.7	128	-1.8	1.32	13.76	-2.1	-34	68
BASE (OPEN)	128	72.6	14.63	73.5	47	113	74.3	128	-1.9	1.31	13.64	-2.1	-34	63
DAY 8 (OPEN)	123	82.8	15.32	83.0	52	135	74.6	123	8.2	1.32	12.45	8.3	-26	49
WEEK 1 (OPEN)	121	80.4	14.04	80.0	46	109	74.6	121	5.8	1.35	12.69	7.0	-22	42
WEEK 2 (OPEN)	121	77.2	13.32	79.0	47	100	74.4	122	3.5	1.06	11.66	4.3	-28	41
WEEK 4 (OPEN)	126	76.5	14.39	76.5	47	109	74.8	126	0.9	1.23	13.84	-0.5	-28	42
WEEK 8 (OPEN)	126	76.5	13.92	73.0	45	113	74.9	126	0.5	1.32	12.80	-0.5	-24	43
WEEK 16 (OPEN)	119	75.5	13.45	74.0	48	115	74.6	119	0.9	1.32	12.19	1.0	-31	42
WEEK 24 (OPEN)	78	75.6	14.39	73.5	48	109	73.8	78	1.8	1.62	14.41	1.7	-25	42
WEEK 40 (OPEN)	16	74.7	16.58	73.0	51	109	75.2	16	-0.7	3.39	13.13	0.1	-21	33
WEEK 52 (OPEN)	1	80.0	1.41	80.0	79	81	62.2	2	17.8	0.69	0.71	17.8	17	18
END POINT (OPEN)	128	76.4	14.31	74.0	49	109	74.7	128	0.7	1.30	13.63	0.0	-31	42
Pali/Pali <=1 months														
BASELINE (DB)	176	77.2	15.04	77.0	46	142								
AVERAGE PREDOSE	176	78.1	13.56	77.7	49	134								
DAY 4 (DB),4H PST	175	85.2	14.79	85.0	52	132	78.2	175	6.9	0.91	12.09	7.7	-19	48
DAY 4 (DB),10H PST	171	84.3	14.46	84.0	50	130	77.7	171	7.2	0.83	10.92	7.0	-32	54
DAY 4 (DB),22H PST	171	82.8	15.33	81.0	48	130	78.2	171	4.6	1.04	13.01	3.7	-32	48
DAY 8 (DB),4H PST	175	81.8	13.31	80.0	50	130	78.0	175	3.8	0.89	11.76	5.1	-29	38
DAY 8 (DB),10H PST	173	81.6	13.13	81.5	49	133	77.7	173	3.9	0.92	12.14	5.7	-33	41
DAY 8 (DB),22H PST	177	81.4	15.67	81.0	44	128	77.9	177	3.5	1.06	13.93	3.7	-26	42
DAY 15 (DB)	24	73.8	14.97	73.5	51	114	76.2	24	-2.5	2.28	11.16	-1.7	-32	18

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DAY 15 (ON),PRE-DS	183	79.4	15.67	78.0	48	135	79.4	182	1.0	1.02	13.84	0.8	-58	45
DAY 15 (ON),1-2H PST	160	82.2	14.84	83.0	56	119	78.6	158	3.9	1.16	14.11	3.7	-52	36
DAY 15 (ON),4H PST	148	81.8	14.16	84.0	60	118	78.7	142	5.1	1.12	13.66	5.1	-40	37
DAY 22 (ON)	161	77.9	13.13	77.0	51	117	78.2	162	-0.4	1.08	13.43	-0.4	-51	36
DAY 36 (ON),PRE-DS	105	77.2	14.92	76.0	44	138	78.5	105	-1.1	1.32	13.48	-0.1	-38	38
DAY 36 (ON),1-2H PST	107	78.1	13.87	79.0	58	112	78.2	107	-0.2	1.35	14.01	-0.1	-46	53
DAY 36 (ON),4H PST	104	79.2	13.43	77.5	56	111	78.0	104	1.1	1.44	14.68	1.2	-52	42
DAY 43 (ON)	127	71.1	11.66	74.0	58	111	77.7	127	-1.6	1.04	11.77	-1.0	-52	36
END POINT (ON)	178	76.8	13.78	76.0	48	111	78.1	178	-1.1	0.93	13.45	-1.7	-52	33
HASH (OPEN)	178	76.8	13.78	76.0	48	111	78.1	178	-1.1	0.92	13.36	-1.6	-52	33
DAY 4 (OPEN)	167	78.5	12.95	78.0	47	119	77.5	167	1.0	1.02	12.74	0.1	-32	37
WEEK 1 (OPEN)	163	77.9	13.64	78.0	52	133	77.8	163	0.0	0.92	11.69	0.7	-52	36
WEEK 2 (OPEN)	136	79.2	12.91	79.0	51	139	78.3	136	1.0	1.19	13.69	1.1	-48	42
WEEK 4 (OPEN)	73	79.4	13.58	78.0	51	114	79.8	72	-0.4	1.37	11.64	-0.2	-42	37
WEEK 8 (OPEN)	13	71.4	10.96	78.0	58	93	77.8	12	-6.5	2.36	10.56	-6.2	-24	13
WEEK 16 (OPEN)	2	91.0	6.08	86.0	76	87	84.1	3	-1.1	6.07	10.63	-6.1	-6	11
WEEK 24 (OPEN)	1	89.0	4.34	89.0	96	102	88.7	2	10.1	9.34	13.30	10.1	1	10
END POINT (OPEN)	173	79.0	14.33	77.0	51	139	77.8	173	1.1	1.01	13.32	1.1	-49	44
Pali/Pali >3 months														
BASELINE (ON)	504	74.6	13.47	76.0	42	133								
AVERAGE PERIOD	504	76.6	13.16	76.2	42	128								
DAY 4 (ON),4H PST	454	81.8	14.36	84.0	42	134	76.7	454	5.2	0.62	11.81	5.1	-32	54
DAY 4 (ON),10H PST	482	81.6	13.86	81.0	46	119	76.7	482	5.0	0.67	12.64	5.0	-40	55
DAY 4 (ON),22H PST	488	78.6	14.06	79.0	44	130	76.8	484	3.7	0.65	13.08	3.7	-32	50
DAY 8 (ON),4H PST	501	81.7	13.61	83.0	47	131	76.7	501	6.0	0.62	11.60	6.1	-26	46
DAY 8 (ON),10H PST	496	79.7	13.30	80.0	46	117	76.6	496	4.1	0.64	11.96	4.0	-27	40
DAY 8 (ON),22H PST	499	77.2	13.84	76.0	44	139	76.7	498	1.6	0.66	12.24	0.7	-38	60
DAY 15 (ON)	24	76.0	15.64	73.5	46	113	70.8	24	4.1	1.83	10.66	5.8	-27	13
DAY 15 (ON),PRE-DS	460	76.4	14.40	76.0	38	133	76.0	460	0.4	0.63	12.71	0.0	-39	53
DAY 15 (ON),1-2H PST	469	79.6	14.58	79.0	48	140	76.9	469	3.6	0.66	14.12	3.7	-44	61
DAY 15 (ON),4H PST	468	81.2	14.98	80.0	42	144	76.8	469	5.3	0.66	14.15	4.1	-28	66
DAY 22 (ON)	472	76.6	13.54	76.0	44	120	76.7	472	-0.1	0.66	12.34	0.0	-40	46
DAY 36 (ON),PRE-DS	393	71.8	14.81	73.0	42	162	76.2	392	-1.1	0.67	13.31	-1.7	-51	75
DAY 36 (ON),1-2H PST	393	76.4	13.82	74.0	44	139	76.0	391	-0.7	0.65	12.86	-0.7	-42	51
DAY 36 (ON),4H PST	389	76.0	13.22	76.0	38	135	76.0	389	-0.1	0.63	12.60	0.0	-37	47
DAY 43 (ON)	414	71.5	13.35	73.0	44	112	76.9	413	-3.0	0.69	12.13	-3.7	-34	37
END POINT (ON)	506	74.3	13.48	73.0	44	117	76.6	504	-1.3	0.66	12.30	-3.0	-24	43
HASH (OPEN)	506	74.0	13.33	73.0	44	114	76.6	504	-1.6	0.65	12.17	-3.1	-24	37
DAY 4 (OPEN)	476	76.5	13.43	74.0	44	119	76.8	475	-0.2	0.59	12.56	-0.7	-41	42
WEEK 1 (OPEN)	487	76.2	12.84	74.0	42	110	76.6	486	-0.3	0.56	12.40	-0.7	-45	51
WEEK 2 (OPEN)	483	76.1	13.11	74.0	44	116	76.7	481	-0.6	0.57	12.53	-1.0	-38	51
WEEK 4 (OPEN)	453	74.7	13.70	74.0	42	119	76.7	453	-1.0	0.57	12.62	-1.0	-40	42
WEEK 8 (OPEN)	471	74.9	14.16	74.0	42	130	76.6	471	-0.9	0.60	12.06	-0.7	-42	42
WEEK 16 (OPEN)	276	76.6	13.17	74.0	44	115	76.2	274	-0.7	0.71	12.79	-0.7	-46	51
WEEK 24 (OPEN)	248	74.5	13.54	74.0	41	114	76.2	248	-1.8	0.87	13.69	-1.7	-38	35
WEEK 40 (OPEN)	60	77.4	14.92	76.5	52	113	74.6	60	1.7	1.92	13.66	1.8	-26	41
WEEK 52 (OPEN)	6	69.5	14.67	63.0	51	95	68.7	5	0.1	2.67	5.75	-0.1	-9	6
END POINT (OPEN)	504	74.4	14.02	73.0	41	119	76.6	503	-1.2	0.67	14.12	-1.7	-42	51
Olan/Pali <3 months														
BASELINE (ON)	106	76.1	14.04	73.5	51	111								
AVERAGE PERIOD	106	77.5	13.63	76.5	47	114								
DAY 4 (ON),4H PST	106	79.4	13.44	76.0	48	113	77.2	106	2.1	1.15	11.92	1.0	-22	44
DAY 4 (ON),10H PST	104	80.0	12.00	79.0	41	110	77.3	104	2.6	1.19	12.04	1.7	-27	44
DAY 4 (ON),22H PST	100	76.0	15.67	76.0	44	115	76.6	100	-0.5	1.11	11.00	-0.7	-28	33
DAY 8 (ON),4H PST	104	81.4	15.76	83.0	50	138	77.2	104	4.2	1.37	12.97	5.0	-29	42
DAY 8 (ON),10H PST	103	80.2	15.68	80.0	46	119	77.2	103	3.1	1.18	12.08	3.0	-27	33
DAY 8 (ON),22H PST	100	76.6	14.64	76.5	48	113	77.2	100	-0.6	1.10	12.02	-0.1	-32	41
DAY 15 (ON),PRE-DS	105	76.5	14.43	76.0	46	116	77.4	105	-1.0	1.13	12.17	-1.7	-30	33
DAY 15 (ON),1-2H PST	101	81.0	15.19	81.0	48	117	77.2	101	3.8	1.30	12.84	4.1	-32	39
DAY 15 (ON),4H PST	99	82.4	16.14	83.0	52	120	77.2	98	5.2	1.35	12.63	4.0	-21	40
DAY 22 (ON)	89	79.7	13.36	79.0	52	111	77.0	89	2.6	1.17	11.01	2.0	-26	38
DAY 36 (ON),PRE-DS	73	74.6	14.38	71.0	58	134	76.2	73	-1.7	1.10	10.31	-4.0	-31	39
DAY 36 (ON),1-2H PST	76	76.8	14.89	76.0	42	138	76.6	76	0.1	1.19	11.39	0.2	-34	31
DAY 36 (ON),4H PST	74	79.5	18.05	79.0	44	139	76.2	74	3.1	1.54	13.31	3.1	-21	45
DAY 43 (ON)	71	76.4	15.44	74.0	44	113	77.1	71	-0.7	1.46	12.37	-1.1	-22	42
END POINT (ON)	106	77.0	15.37	76.5	44	115	77.6	106	-0.6	1.34	12.72	-1.7	-32	42
HASH (OPEN)	106	76.6	14.75	76.0	44	113	77.6	106	-0.9	1.30	12.32	-1.0	-29	42
DAY 4 (OPEN)	89	86.9	16.40	88.0	58	132	77.9	89	8.9	1.55	14.63	9.1	-27	44
WEEK 1 (OPEN)	90	81.6	15.00	81.0	52	127	76.8	90	5.8	1.30	12.36	6.1	-22	46
WEEK 2 (OPEN)	78	81.9	13.67	80.0	54	142	77.1	78	4.7	1.48	13.11	3.8	-26	57
WEEK 4 (OPEN)	66	76.8	14.09	76.0	51	134	77.8	66	-3.0	1.84	13.66	-4.0	-30	32
WEEK 8 (OPEN)	21	79.9	13.59	81.0	60	102	77.9	22	3.1	2.82	13.16	3.4	-34	39
WEEK 16 (OPEN)	1	64.0		64.0	64	64	86.0	1	-21.0			-21.0	-21	-21
END POINT (OPEN)	102	78.3	15.86	76.0	50	136	77.6	102	0.7	1.32	13.63	-0.7	-27	42
Olan/Pali >3 months														
BASELINE (ON)	142	76.2	13.39	76.0	48	114								
AVERAGE PERIOD	142	77.6	11.43	78.0	49	111								
DAY 4 (ON),4H PST	139	79.2	14.82	77.0	46	134	77.5	139	1.8	1.09	12.83	1.0	-32	40
DAY 4 (ON),10H PST	136	80.1	14.11	78.0	47	115	77.4	136	1.7	1.15	13.39	1.7	-20	51
DAY 4 (ON),22H PST	138	76.9	13.49	76.0	47	111	77.4	138	-1.5	1.02	12.03	-1.1	-22	34
DAY 8 (ON),4H PST	139	79.2	12.76	78.0	52	111	77.6	139	1.7	1.14	13.48	1.7	-28	32
DAY 8 (ON),10H PST	138	79.2	12.81	80.0	50	114	77.5	138	1.9	1.15	13.64	1.7	-42	51
DAY 8 (ON),22H PST	141	76.6	12.30	76.0	42	103	77.6	141	-0.9	1.01	11.95	-1.0	-28	35
DAY 15 (ON),PRE-DS	140	76.4	12.84	76.0	51	103	77.6	140	-1.1	0.99	11.78	-1.0	-25	34
DAY 15 (ON),1-2H PST	139	80.4	14.37	80.0	52	116	77.5	139	3.9	1.34	14.57	3.0	-25	49
DAY 15 (ON),4H PST	139	80.8	14.63	81.0	54	114	77.5	139	3.3	1.32	15.18	3.7	-24	44
DAY 22 (ON)	126	79.8	12.74	79.0	56	122	77.2	126	3.6	1.18	14.48	3.6	-34	60
DAY 36 (ON),PRE-DS	121	76.0	12.45	74.0	50	115	77.2	121	-2.2	1.12	13.56	-3.1	-35	32
DAY 36 (ON),1-2H PST	120	76.1	12.54	76.0	48	105	77.1	120	-1.0	1.10	13.13	-0.7	-29	37
DAY 36 (ON),4H PST	120	76.6	13.19	76.5	54	113	77.1	120	-0.5	1.19	13.47	-0.1	-29	37
DAY 43 (ON)	123	74.4	11.67	74.5	52	109	77.0	122	-3.6	1.10	12.10	-3.0	-26	29
END POINT (ON)	142	76.8	11.60	76.0	52	109	77.5	142	-1.7	1.02	13.35	-3.7	-26	31
HASH (OPEN)	142	76.6	11.42	76.0	52	109	77.5	142	-1.9	1.00	11.94	-3.7	-25	29
DAY 4 (OPEN)	116	84.9	13.36	86.0	56	115	77.2	116	7.6	1.33	14.14	8.0	-24	45
WEEK 1 (OPEN)	116	82.6	13.67	81.0	56	117	77.4	116	5.1	1.19	13.82	4.1	-37	53
WEEK 2 (OPEN)	113	79.4	13.23	76.5	56	109	77.2	113	2.3	1.34	13.96	1.7	-22	35
WEEK 4 (OPEN)	100	78.4	13.86	77.0	48	114	77.3	100	1.2	1.38	13.93	0.0	-26	38
WEEK 8 (OPEN)	100	78.4	14.82	77.5	48	126	77.5	100	0.9	1.36	14.86	-0.5	-32	62
WEEK 16 (OPEN)	124	77.8	15.19	74.0	47	137	77.5	124	0.2	1.30	14.61	0.3	-20	53
WEEK 24 (OPEN)	94	74.9	14.53	74.0	45	115	77.0	94	-3.3	1.71	15.69	-3.2	-34	41
WEEK 40 (OPEN)	16	72.2	17.55	68.5	51	106	77.1	16	-4.9	2.86	11.44	-4.2	-32	12
END POINT (OPEN)	143	77.1	15.00	76.0	45	119	77.6	143	-0.4	1.31	14.50	-0.7	-34	41

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Note the DB-olanzapine/OL-Pal subgroups showed group mean increases in heart rate after switching from DB olanzapine to OL-Pal. It is not clear if this observation is reflecting an interruption of treatment between the DB and OL trials, or a differential drug or dose-level effect on heart rate between these two drugs (e.g. Pal may induce greater effects on heart rate than olanzapine or the dose-level of Pal may results in greater exposure to active drug than exposure to olanzapine at the doses employed). However, the dose-equivalency between olanzapine is Pal is not clear. Therefore, results of active drug comparisons are difficult to interpret.

Similar observations are described in this review under Section 7.1.8 on vital sign results.

II. Clinically Unremarkable Pal-Group Mean Increase in PR Interval *As observed in the short-term trial dataset, the group mean PR interval numerically increased (from the pre-dose average value) during Pal treatment in subjects switched from DB Olanzapine to OL Pal treatment and subjects switched from DB-placebo to OL Pal. However, the group mean increases were clinically unremarkable in the magnitude of this apparent drug-effect and mean increases generally did not appear to increase over time for at least up to week 24 of OL treatment (where samples sizes were over 50 subjects).*

III. Pal Group Mean Decreases in RR Interval

As observed in the short-term trial dataset, RR interval results show group mean decreases in RR interval as shown below (selected sections are taken from appendix 2.7.4.6.2.2 of the SCS). The numerical mean decreases generally, did not appear to increase in magnitude over time during OL treatment for at least up to week 24 of OL treatment (where samples sizes were over 50 subjects).

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output EGCGD1, ECG, Means and Mean Changes from Pre-treatment over Time - Open-Label Phase

Analysis Set: Safety

							Data	change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
HEART RATE (beats/min)														

XR (ms)													
Pts/Full <=1 months													
BASELINE (DB)	107	827.1	119.81	221.0	628	1277							
AVERAGE PREDOSE	107	821.8	110.58	211.7	622	1162							
DAY 4 (DB),4H PST	106	817.7	128.92	211.0	571	1200	824.4	105	-16.7	12.39	134.55	-10.1	-424 281
DAY 4 (DB),10H PST	104	828.1	142.66	216.5	617	1164	823.1	104	-5.0	12.10	124.63	-13.0	-358 331
DAY 4 (DB),22H PST	103	831.7	141.03	217.0	600	1266	836.4	102	36.1	15.72	139.43	44.7	-315 358
DAY 8 (DB),4H PST	106	828.5	147.17	227.5	496	1277	832.5	106	-4.0	13.26	137.44	-3.8	-500 462
DAY 8 (DB),10H PST	106	816.8	136.94	211.0	525	1132	822.8	106	-16.0	12.32	134.31	-23.7	-388 314
DAY 8 (DB),22H PST	106	842.2	166.40	246.0	583	1333	822.8	106	29.5	12.69	129.67	21.2	-298 498
DAY 15 (DB)	21	924.2	135.67	956.0	682	1234	852.2	21	71.8	17.65	136.34	47.1	-335 468
DAY 15 (DB),PRE-DS	86	840.4	164.44	967.0	522	1234	827.9	86	13.4	15.02	138.68	11.0	-377 439
DAY 15 (DB),1-2H PST	86	799.5	148.63	789.0	560	1260	828.1	86	-28.6	16.02	147.73	-24.0	-480 288
DAY 15 (DB),4H PST	86	801.2	142.54	789.0	560	1255	827.8	86	-26.8	16.12	148.60	-25.1	-480 332
DAY 29 (DB)	86	827.8	146.15	913.0	522	1176	830.0	86	-3.1	14.86	134.38	-16.0	-342 337
DAY 36 (DB),PRE-DS	36	853.7	168.37	961.0	594	1260	835.2	36	24.4	22.89	137.35	18.0	-247 395
DAY 36 (DB),1-2H PST	36	801.4	139.68	794.5	594	1111	823.4	36	-23.1	20.04	133.66	-25.9	-239 269
DAY 36 (DB),4H PST	36	819.7	138.47	911.0	594	1132	824.7	36	-15.0	22.41	134.45	-37.7	-236 349
DAY 43 (DB)	82	836.8	146.32	983.0	582	1234	863.1	82	33.7	19.60	141.36	17.0	-274 403
END POINT (DB)	107	821.6	123.27	923.0	600	1234	821.8	107	-10.1	14.46	149.58	-13.0	-346 405
BASE (OPEN)	107	829.6	165.77	923.0	600	1234	821.8	107	-8.2	14.16	147.46	-9.7	-343 460
DAY 4 (OPEN)	97	760.5	157.01	741.0	465	1233	834.7	97	-78.2	15.72	154.83	-66.1	-463 402
WEEK 1 (OPEN)	96	747.8	136.94	741.0	536	1071	834.0	96	-86.3	13.46	131.30	-86.3	-406 284
WEEK 2 (OPEN)	90	767.0	139.78	760.0	526	1111	824.7	90	-67.7	13.42	137.37	-71.7	-320 286
WEEK 4 (OPEN)	74	817.6	178.27	794.5	541	1413	821.4	74	-13.8	17.22	149.00	7.0	-346 492
WEEK 8 (OPEN)	36	808.2	161.11	789.0	522	1234	861.7	36	6.6	32.21	137.39	-3.0	-326 349
WEEK 16 (OPEN)	1	989.0		989.0	989	989	782.7	1	206.1			206.1	206 206
END POINT (OPEN)	106	813.2	158.91	900.0	522	1413	824.4	106	-21.2	14.32	146.36	-23.5	-346 493
Pts/Full >1 months													
BASELINE (DB)	128	840.9	142.96	927.5	526	1234							
AVERAGE PREDOSE	128	828.2	130.79	901.8	582	1232							
DAY 4 (DB),4H PST	125	807.7	153.15	789.0	465	1234	826.8	125	-18.8	11.33	136.69	-21.7	-462 337
DAY 4 (DB),10H PST	125	828.9	167.88	900.0	472	1233	831.5	125	-3.6	12.12	135.47	-3.7	-474 460
DAY 4 (DB),22H PST	125	854.1	160.04	946.0	532	1272	859.7	125	26.4	10.91	131.92	24.6	-284 506
DAY 8 (DB),4H PST	127	822.6	146.77	911.0	566	1272	829.2	127	-6.7	12.42	139.92	-1.3	-431 484
DAY 8 (DB),10H PST	126	850.2	162.13	921.0	531	1233	831.1	126	19.1	12.42	140.71	8.1	-434 431
DAY 8 (DB),22H PST	125	840.9	164.54	946.0	566	1296	828.7	125	21.2	12.86	141.65	28.7	-438 386
DAY 15 (DB)	9	851.4	162.34	967.0	618	1071	858.6	9	-7.1	34.88	184.65	-62.7	-385 360
DAY 15 (DB),PRE-DS	116	846.0	179.14	970.0	526	1422	828.3	116	27.7	14.36	154.69	18.2	-569 749
DAY 15 (DB),1-2H PST	117	836.3	163.87	923.0	550	1500	827.9	117	7.4	14.86	160.68	-3.7	-487 637
DAY 15 (DB),4H PST	118	836.3	170.94	923.0	465	1500	826.4	118	9.9	14.18	154.03	-1.7	-394 637
DAY 29 (DB)	106	831.2	158.43	922.0	526	1200	827.6	106	-4.4	15.76	161.44	-8.0	-692 292
DAY 36 (DB),PRE-DS	75	859.4	190.33	911.0	631	1277	830.4	75	29.4	18.64	164.76	11.7	-500 439
DAY 36 (DB),1-2H PST	78	836.6	176.83	911.0	594	1260	827.2	78	8.7	19.39	170.40	5.2	-578 446
DAY 36 (DB),4H PST	78	840.2	168.70	789.0	541	1232	827.9	78	12.1	20.26	179.75	11.8	-567 434
DAY 43 (DB)	58	871.9	172.43	967.5	594	1277	821.0	58	38.8	14.58	140.67	40.1	-320 369
END POINT (DB)	128	836.7	176.44	915.0	526	1277	828.2	128	28.4	12.58	158.17	21.6	-692 367
BASE (OPEN)	128	857.9	174.69	919.0	536	1272	828.2	128	29.6	12.92	167.60	21.6	-692 367
DAY 4 (OPEN)	123	750.2	141.02	733.0	480	1132	830.9	123	-80.5	11.30	134.34	-78.0	-526 265
WEEK 1 (OPEN)	121	770.6	142.53	760.0	550	1204	830.2	121	-59.7	12.39	135.30	-66.0	-428 339
WEEK 2 (OPEN)	122	794.9	148.46	769.0	554	1277	831.7	122	-37.0	12.31	135.96	-46.9	-443 364
WEEK 4 (OPEN)	126	822.2	163.64	794.5	554	1277	826.5	126	-4.3	13.52	154.35	-0.8	-472 360
WEEK 8 (OPEN)	126	822.1	162.05	921.0	604	1232	826.2	126	-4.1	12.38	149.59	-1.0	-412 382
WEEK 16 (OPEN)	115	819.4	149.61	911.0	532	1234	820.1	115	-10.7	12.01	141.56	-9.7	-440 366
WEEK 24 (OPEN)	78	821.0	161.72	916.5	550	1234	829.4	78	-18.4	18.71	165.16	-19.7	-670 367
WEEK 40 (OPEN)	15	841.9	184.32	933.0	554	1176	826.0	15	16.9	37.14	144.01	-19.0	-387 291
WEEK 52 (OPEN)	1	750.0	12.73	750.0	741	759	975.0	2	-225.0	8.67	12.26	-225.0	-234 -216
END POINT (OPEN)	128	821.4	162.54	911.0	550	1234	828.2	128	-6.9	12.12	149.70	-1.5	-670 336
Pall/Pall <=1 months													
BASELINE (DB)	178	806.6	160.62	779.0	402	1204							
AVERAGE PREDOSE	178	796.5	135.67	780.0	452	1238							
DAY 4 (DB),4H PST	175	716.9	156.06	706.0	448	1132	795.2	175	-78.4	6.19	104.35	-73.1	-359 164
DAY 4 (DB),10H PST	171	728.0	127.93	714.0	442	1200	799.6	171	-71.8	7.65	99.67	-71.0	-367 264
DAY 4 (DB),22H PST	171	750.0	142.62	733.0	500	1260	794.0	171	-44.0	6.79	112.74	-19.8	-342 138
DAY 8 (DB),4H PST	175	724.9	125.05	706.0	442	1200	796.4	175	-61.9	6.62	112.73	-63.0	-372 261
DAY 8 (DB),10H PST	173	727.1	122.62	718.5	498	1234	800.5	173	-63.4	8.31	119.43	-69.5	-454 165
DAY 8 (DB),22H PST	177	751.8	156.35	741.0	468	1264	797.8	177	-36.0	8.86	131.46	-10.1	-422 183
DAY 15 (DB)	24	844.6	178.60	916.5	536	1176	817.1	24	27.6	17.89	132.72	11.1	-225 261
DAY 15 (DB),PRE-DS	163	794.0	168.40	765.0	498	1234	793.5	163	-8.5	9.63	137.61	-13.7	-412 266
DAY 15 (DB),1-2H PST	160	750.6	132.14	721.0	504	1051	792.2	160	-41.7	10.79	132.11	-46.7	-380 279
DAY 15 (DB),4H PST	149	737.5	131.99	714.0	508	1200	789.2	149	-51.8	10.46	137.68	-46.7	-446 259
DAY 29 (DB)	163	791.3	135.17	779.0	512	1176	791.2	163	-0.0	20.12	137.32	1.1	-306 133
DAY 36 (DB),PRE-DS	105	804.1	149.07	789.0	526	1264	790.6	105	13.6	13.19	137.09	-0.7	-254 162
DAY 36 (DB),1-2H PST	107	789.2	130.01	769.0	492	1260	792.2	107	-2.1	12.48	132.00	-1.2	-380 254
DAY 36 (DB),4H PST	104	795.2	132.17	774.0	541	1071	791.2	104	-20.0	12.12	134.85	-24.0	-352 279
DAY 43 (DB)	127	817.2	122.75	811.6	496	1200	798.5	127	18.7	10.62	119.60	21.0	-295 195
END POINT (DB)	178	802.7	131.40	800.0	496	1260	796.5	178	6.2	9.39	135.36	11.1	-311 196
BASE (OPEN)	178	802.4	131.58	800.0	496	1260	796.5	178	6.0	9.35	133.47	11.1	-295 196
DAY 4 (OPEN)	167	785.4	132.83	769.0	504	1277	801.1	167	-15.7	10.33	132.44	-9.0	-377 282
WEEK 1 (OPEN)	163	791.2	135.33	769.0	451	1184	798.1	163	-8.9	9.02	116.30	-11.7	-299 319
WEEK 2 (OPEN)	136	776.4	122.09	769.0	492	1176	792.9	136	-16.5	11.46	132.61	-11.0	-429 180
WEEK 4 (OPEN)	73	777.0	131.63	769.0	526	1176	796.4	73	1.6	13.19	111.18	-1.0	-252 180
WEEK 8 (OPEN)	11	864.7	114.49	867.5	645	1014	802.2	12	53.4	27.04	119.22	46.3	-217 247
WEEK 16 (OPEN)	3	726.7	54.52	698.0	680	780	724.7	3	1.0	62.37	92.84	61.0	-106 59
WEEK 24 (OPEN)	1	696.0	26.16	696.0	696	696	696.2	2	-78.7	71.32	100.84	-78.7	-150 -7
END POINT (OPEN)	173	791.1	134.60	779.0	492	1176	798.0	173	-14.9	10.06	132.17	-19.0	-429 180
Pall/Pall >1 months													
BASELINE (DB)	504	822.3	160.16	900.0	474	1439							
AVERAGE PREDOSE	504	821.2	132.13	796.8	511	1439							
DAY 4 (DB),4H PST	454	727.0	134.77	714.0	484	1295	820.7	454	-93.7	5.44	130.84	-91.8	-542 173
DAY 4 (DB),10H PST	483	768.5	136.32	741.0	504	1264	820.3	483	-51.8	5.55	136.67	-51.7	-474 184
DAY 4 (DB),22H PST	484	779.5	146.72	759.0	560	1264	819.4	484	-39.9	5.80	137.66	-30.7	-471 434
DAY 8 (DB),4H PST	501	796.2	131.86	781.0	496	1277	828.7	501	-68.5	5.42	131.35	-69.7	-525 310
DAY 8 (DB),10H PST	456	774.1	132.04	760.0	512	1264	823.3	456	-47.5	5.67	134.35	-42.0	-489 142
DAY 8 (DB),22H PST	499	802.7	147.74	789.0	465	1264	820.8	499	-18.3	5.91	131.92	-16.4	-520 181
DAY 15 (DB)	34	832.4	178.58	927.5	531	1264	832.2	34	-29.4	18.93	136.44	-51.5	-386 276
DAY 15 (DB),PRE-DS	460	811.0	152.17	900.0	459	1439	817.8	460	-8.5	6.17	136.49	-8.3	-464 608
DAY 15 (DB),1-2H PST	459	791.6	132.01	769.0	474	1500	818.1	459	-26.6	7.04	150.75	-18.2	-669 464
DAY 15 (DB),4H PST	460	761.1	142.64	760.0	417	1413	816.9	459	-61.7	6.80	145.66	-46.7	-739 582
DAY 29 (DB)	473	821.9	156.39	900.0	500	1264	820.9	472	0.6	6.17	133.56	-8.4	-442 432
DAY 36 (DB),PRE-DS	393	841.9	162.37	913.0	358	1295	816.5	392	28.4	7.12	141.39	21.8	-366 431
DAY 36 (DB),1-2H PST	391	822.7	151.61	911.0	432	1264	817.0	391	8.9	6.54	133.33	1.7	-292 434
DAY 36 (DB),4H PST	385	814.7	146.62	900.0	444	1519	816.9	388	-2.2	6.92	136.67	-7.8	-347 602
DAY 43 (DB)	414	839.6	160.60	913.0	531	1264	819.2	413	20.1	6.37	132.63	24.0	-491 419

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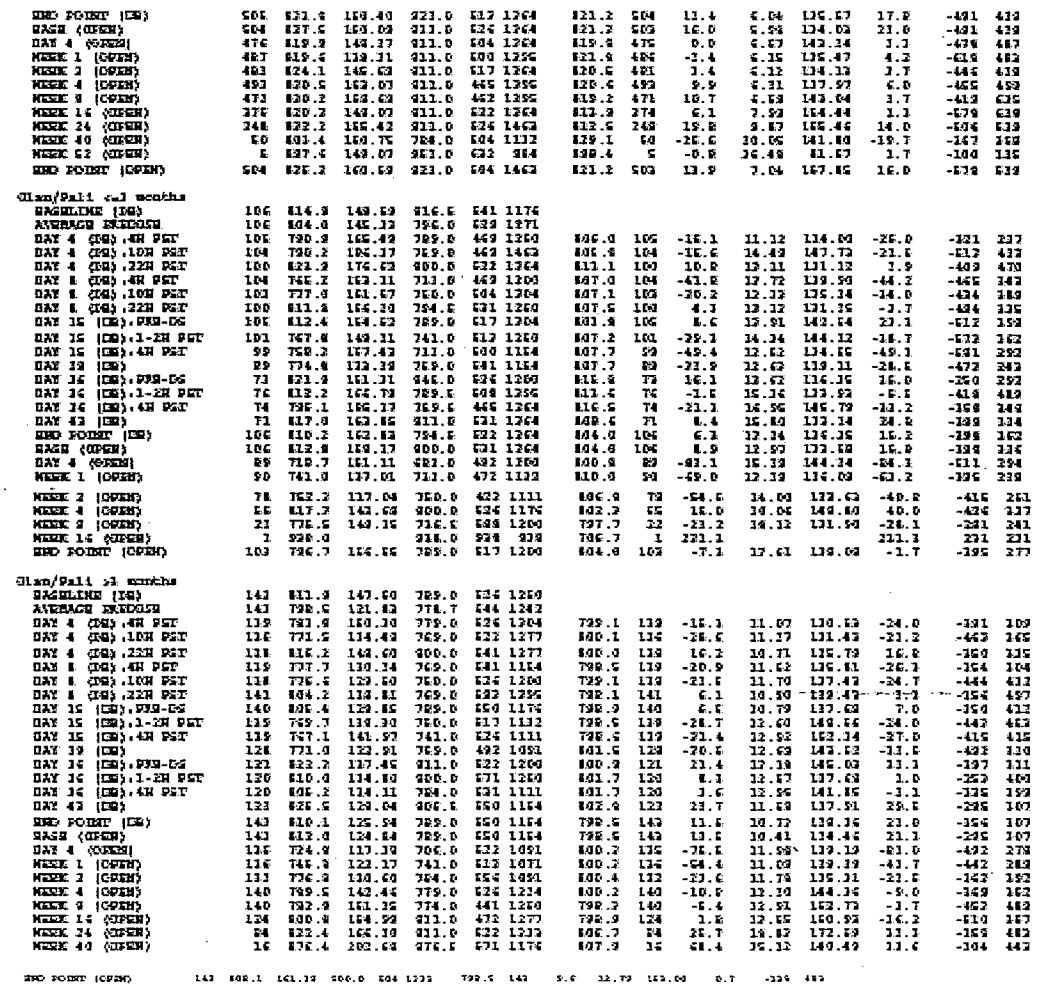

END POINT (EP)	505	821.6	158.40	923.0	512	1264	821.2	504	11.4	6.84	135.67	17.8	-491	428
BASE (OPEN)	504	827.5	153.02	911.0	524	1264	821.2	503	16.0	6.56	134.06	21.0	-481	428
DAY 4 (%FREE)	476	819.9	148.27	911.0	504	1264	819.8	476	0.0	6.67	143.34	1.1	-479	467
WEEK 1 (OPEN)	487	819.6	138.31	911.0	500	1256	821.8	486	-3.4	6.35	135.47	4.2	-431	462
WEEK 2 (OPEN)	483	824.1	146.63	911.0	517	1264	820.6	481	3.4	6.32	134.13	3.7	-446	439
WEEK 4 (OPEN)	493	820.5	152.07	911.0	445	1256	820.6	493	9.9	6.31	137.97	6.0	-455	452
WEEK 8 (OPEN)	473	830.2	158.62	911.0	462	1256	819.2	471	10.7	6.58	143.04	3.7	-413	435
WEEK 16 (UPEN)	376	820.2	142.02	911.0	522	1264	812.8	374	6.1	7.52	154.44	1.1	-479	439
WEEK 24 (UPEN)	348	822.2	155.42	911.0	526	1462	812.6	348	15.8	8.67	155.46	14.0	-506	539
WEEK 40 (UPEN)	50	803.4	160.75	788.0	504	1112	839.1	50	-25.6	30.05	141.80	-19.7	-167	168
WEEK 52 (UPEN)	5	837.6	148.07	951.0	652	914	838.4	5	-0.8	36.48	81.57	1.7	-100	135
END POINT (OPEN)	504	825.2	160.69	923.0	504	1462	821.2	503	13.9	7.04	167.85	16.0	-578	539
Olan/Pal1 <=1 months														
BASELINE (DB)	106	814.9	148.59	916.5	541	1176								
AVERAGE KNEDOSE	106	804.0	145.33	796.0	539	1271								
DAY 4 (DB),4H PST	105	790.9	166.42	789.0	469	1260	806.0	105	-15.1	11.12	114.04	-26.0	-321	237
DAY 4 (DB),10H PST	104	796.2	156.37	769.0	462	1462	805.9	104	-15.6	14.43	147.72	-21.5	-312	412
DAY 4 (DB),22H PST	100	822.9	176.63	800.0	532	1364	811.1	100	10.8	13.11	131.12	7.9	-403	470
DAY 8 (DB),4H PST	104	766.2	153.11	711.0	469	1260	807.0	104	-41.8	17.72	139.90	-44.2	-465	343
DAY 8 (DB),10H PST	103	777.0	161.67	769.0	504	1364	807.1	105	-30.2	12.12	125.34	-34.0	-434	369
DAY 8 (DB),22H PST	100	811.8	164.30	784.5	531	1260	807.5	100	4.3	13.12	131.35	-3.7	-434	335
DAY 15 (DB),END-DS	105	812.4	164.62	789.0	517	1304	803.9	105	8.6	15.91	162.54	23.1	-512	352
DAY 15 (DB),1-2H PST	101	767.8	149.11	741.0	512	1260	807.2	101	-29.3	14.34	144.12	-18.7	-532	162
DAY 15 (DB),4H PST	99	758.3	157.43	711.0	500	1164	807.7	99	-49.4	12.62	124.55	-49.1	-531	292
DAY 29 (DB)	89	774.4	133.39	769.0	541	1164	807.7	89	-33.3	12.62	119.11	-28.5	-472	243
DAY 36 (DB),END-DS	73	823.9	161.31	946.0	526	1260	816.9	73	16.1	13.62	116.35	16.0	-350	292
DAY 36 (DB),1-2H PST	76	813.2	166.79	789.5	508	1256	811.5	76	-1.5	15.36	133.85	-5.5	-418	412
DAY 36 (DB),4H PST	74	796.1	186.17	769.5	445	1264	816.5	74	-21.1	16.56	145.79	-12.2	-368	249
DAY 43 (DB)	71	817.0	163.65	811.0	531	1364	808.6	71	8.4	15.80	133.14	20.0	-388	334
END POINT (DB)	106	810.2	162.83	784.5	522	1364	804.0	106	6.3	12.34	134.35	15.2	-398	362
BASE (OPEN)	106	812.8	159.17	800.0	531	1264	804.0	106	8.9	12.93	133.58	16.8	-398	336
DAY 4 (%FREE)	89	718.7	161.11	681.0	492	1260	800.8	89	-83.1	16.33	144.34	-84.1	-511	294
WEEK 1 (OPEN)	90	741.0	137.01	711.0	472	1132	810.8	90	-69.0	12.39	116.09	-63.2	-396	238
WEEK 2 (OPEN)	78	752.2	137.04	750.0	452	1111	806.9	78	-54.6	14.03	122.63	-49.8	-416	261
WEEK 4 (OPEN)	66	817.3	143.62	800.0	526	1176	802.2	65	15.0	10.06	140.80	40.0	-426	337
WEEK 8 (OPEN)	21	776.5	149.15	716.5	588	1200	797.7	22	-23.2	18.12	131.58	-26.1	-281	241
WEEK 16 (UPEN)	1	928.0		928.0	928	928	796.7	1	221.1			221.3	231	231
END POINT (OPEN)	103	796.7	156.55	789.0	517	1200	804.0	103	-7.3	17.61	139.09	-1.7	-395	277
Olan/Pal1 >1 months														
BASELINE (DB)	143	811.8	147.60	789.0	536	1260								
AVERAGE KNEDOSE	143	798.5	121.83	778.7	544	1242								
DAY 4 (DB),4H PST	139	783.8	160.30	779.0	526	1304	795.1	139	-15.1	11.07	130.59	-24.0	-391	109
DAY 4 (DB),10H PST	136	771.5	134.48	769.0	522	1277	800.1	136	-28.6	11.17	131.43	-21.2	-463	165
DAY 4 (DB),22H PST	131	816.2	148.60	800.0	541	1277	800.0	130	16.2	10.71	125.79	16.8	-360	335
DAY 8 (DB),4H PST	139	737.7	130.34	769.0	541	1164	798.5	139	-20.9	11.62	136.81	-26.3	-364	104
DAY 8 (DB),10H PST	138	736.6	129.60	760.0	526	1200	799.1	139	-21.5	11.70	137.43	-24.7	-444	432
DAY 8 (DB),22H PST	141	804.2	134.81	769.0	522	1295	798.1	141	6.1	10.50	232.43	-3.2	-356	497
DAY 15 (DB),END-DS	140	806.4	129.85	789.0	550	1176	798.9	140	6.5	10.79	137.68	7.0	-350	412
DAY 15 (DB),1-2H PST	135	769.7	139.30	760.0	517	1132	798.6	139	-28.7	12.60	148.66	-34.0	-443	463
DAY 15 (DB),4H PST	139	767.1	141.97	741.0	526	1111	798.5	139	-31.4	12.52	152.34	-27.0	-415	415
DAY 29 (DB)	128	771.0	122.91	769.0	492	1052	801.6	128	-30.6	12.69	143.52	-31.5	-435	130
DAY 36 (DB),END-DS	121	822.2	137.45	811.0	522	1200	800.8	121	21.4	12.18	146.03	33.3	-197	331
DAY 36 (DB),1-2H PST	120	810.0	134.80	800.0	571	1260	801.7	120	8.3	12.57	137.63	1.0	-259	400
DAY 36 (DB),4H PST	120	806.2	134.11	784.0	531	1111	801.7	120	3.6	12.56	141.85	-3.1	-335	199
DAY 43 (DB)	123	826.5	129.04	806.5	550	1164	802.6	123	23.7	11.68	137.91	25.5	-295	307
END POINT (DB)	143	810.1	125.94	789.0	550	1164	798.6	143	11.5	10.72	138.36	23.0	-356	307
BASE (OPEN)	143	812.0	126.84	789.0	550	1164	798.6	143	13.5	10.41	134.46	21.1	-295	307
DAY 4 (%FREE)	136	724.9	117.39	706.0	522	1052	800.2	135	-75.5	11.98	139.19	-81.0	-492	278
WEEK 1 (OPEN)	136	746.9	122.17	741.0	513	1071	800.2	136	-54.4	11.08	139.39	-43.7	-442	282
WEEK 2 (OPEN)	133	736.8	130.60	784.0	554	1052	800.4	132	-63.6	11.76	135.31	-21.5	-363	352
WEEK 4 (OPEN)	140	789.5	142.46	779.0	526	1234	800.2	140	-10.9	12.10	144.35	-5.0	-369	162
WEEK 8 (OPEN)	140	792.8	161.35	774.0	441	1260	798.5	140	-5.4	12.91	152.73	-1.7	-462	482
WEEK 16 (UPEN)	124	800.8	164.92	811.0	472	1277	798.9	124	1.8	12.65	160.93	-16.2	-410	167
WEEK 24 (UPEN)	84	822.4	166.38	811.0	522	1232	806.7	84	25.7	14.82	172.59	33.3	-355	483
WEEK 40 (UPEN)	16	836.4	202.64	876.5	571	1176	807.9	16	48.4	35.13	140.49	33.6	-304	442
END POINT (OPEN)	143	808.1	161.32	800.0	504	1231	798.6	143	9.6	32.79	163.66	8.7	-326	483

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IV. QTc Interval Results

A. Pal Group Mean QTcBazett's Interval Results *See selected results below showing group mean increases in QTc Bazetts Interval during OL Pal treatment for the subgroups that previously received DB placebo or DB olanzapine in the lead-in studies. It is difficult to interpret the magnitude of QTcB prolongation in the subgroups showing this effect given the previously discussed limitations using the QTcB method.*

Negligible to absent QTB prolongation occurred during OL Pal treatment in the subgroup that previously received DB Pal treatment.

Failure to show remarkable group mean increases during OL Pal in the subgroup that previously received DB Pal may be due to the timing of the assessments which was not held constant relative to dosing and varied across subjects given the nature of this outpatient OL longterm study (as previously discussed under Section 7.1.X. of this review). These OL studies

were not designed to capture ECG drug effects at Tmax (given the outpatient nature of the study and assessment time-point variation across individuals and relative to dosing at least for outpatient study days). Furthermore, a flexible dose regimen was employed and finally a placebo control group was not included.

Results below are taken form appendix 2.7.4.6.2.2 of the SCS.

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DSNG01. ECG. Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base	change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SD	SD	Med	Min	Max
QTC INTERVAL BAZETT (ms)														
Pln/Pall <3 months														
BASELINE (DB)	107	411.6	22.78	413.0	342	468								
AVERAGE PREDOSE	107	412.2	22.06	413.7	360	474								
DAY 4 (DB).4H PST	106	412.0	21.86	410.0	370	474	412.7	106	-0.7	1.64	16.86	-1.0	-39	53
DAY 4 (DB).10H PST	104	413.0	21.91	411.0	366	471	413.1	104	-1.1	1.78	18.17	-1.7	-48	78
DAY 4 (DB).22H PST	103	412.1	23.03	413.0	352	472	413.1	102	-1.0	1.60	16.12	-1.7	-32	47
DAY 8 (DB).4H PST	106	410.9	22.12	412.5	335	456	412.6	106	-3.1	1.65	17.11	-1.8	-45	62
DAY 8 (DB).10H PST	106	412.4	23.30	414.0	341	468	412.5	106	-0.0	1.82	18.73	-1.2	-44	69
DAY 8 (DB).22H PST	106	413.0	23.30	413.0	356	469	412.5	106	0.5	1.82	18.73	0.7	-44	75
DAY 15 (DB)	21	421.7	19.33	421.0	370	451	427.2	21	-6.3	4.60	21.08	-7.7	-64	33
DAY 15 (DB).PRE-DS	84	408.6	25.30	407.5	351	468	409.1	84	-0.6	2.10	19.32	1.8	-60	63
DAY 15 (DB).1-2H PST	85	406.9	23.70	406.0	352	452	408.6	85	-1.8	2.12	19.61	-1.1	-46	68
DAY 15 (DB).4H PST	85	408.7	22.33	409.0	357	465	408.7	85	0.1	1.96	18.04	-0.1	-37	65
DAY 29 (DB)	85	415.0	23.33	416.0	362	469	413.9	85	1.1	2.06	18.94	2.1	-52	60
DAY 36 (DB).PRE-DS	16	406.1	27.30	401.0	362	462	406.6	16	-1.5	3.44	30.66	-1.2	-46	49
DAY 36 (DB).1-2H PST	18	407.7	24.24	409.5	344	460	406.8	18	1.9	3.14	30.06	1.9	-40	35
DAY 36 (DB).4H PST	16	407.8	22.84	408.5	356	458	406.0	16	1.9	3.02	28.36	-1.3	-32	64
DAY 43 (DB)	83	408.6	22.99	407.0	361	468	409.8	83	-1.1	2.07	18.81	-1.1	-58	34
MAXIMUM VALUE (DB)	107	432.8	21.39	436.0	382	492	412.2	107	20.5	1.61	16.70	18.1	-10	75
END POINT (DB)	107	413.9	22.71	415.0	361	460	412.2	107	1.6	1.76	18.18	1.0	-58	57
BASE (OPEN)	107	413.6	22.86	415.0	361	460	412.2	107	1.5	1.72	17.82	1.5	-58	57
DAY 4 (OPEN)	96	422.2	23.76	427.0	366	477	412.6	96	9.4	2.01	19.67	10.7	-46	66
WEEK 1 (OPEN)	96	421.2	25.45	421.0	368	490	411.8	96	9.5	1.94	18.87	11.1	-47	63
WEEK 2 (OPEN)	89	420.2	23.12	423.0	352	474	413.7	89	6.6	1.82	17.25	6.7	-38	68
WEEK 4 (OPEN)	73	414.2	24.74	416.0	328	466	414.4	73	-0.2	2.60	21.24	1.1	-57	62
WEEK 8 (OPEN)	35	418.2	24.09	417.0	367	455	416.2	35	2.0	4.14	24.42	1.1	-62	70
WEEK 16 (OPEN)	1	402.0		402.0	402	402	418.7	1	-16.7			-16.7	-17	-17
MAXIMUM VALUE (OPEN)	106	422.4	23.49	421.5	352	490	412.2	106	20.2	1.62	16.81	18.8	-39	70
END POINT (OPEN)	106	414.2	25.67	416.0	328	456	412.2	106	3.6	2.02	20.90	1.9	-57	70
Pln/Pall >3 months														
BASELINE (DB)	128	406.2	23.17	406.0	342	458								
AVERAGE PREDOSE	128	407.0	20.32	406.7	339	455								
DAY 4 (DB).4H PST	125	407.0	21.45	407.0	352	465	407.2	125	-0.2	1.42	15.97	-1.0	-42	44
DAY 4 (DB).10H PST	125	406.1	22.32	406.0	341	461	406.9	125	-1.8	1.68	17.70	-1.7	-59	49
DAY 4 (DB).22H PST	125	406.2	22.68	406.0	346	460	407.2	125	-1.0	1.46	16.34	-1.7	-46	49
DAY 8 (DB).4H PST	127	404.4	21.82	406.0	335	447	407.0	127	-3.6	1.49	16.79	-1.0	-59	42
DAY 8 (DB).10H PST	126	403.9	22.91	403.0	340	455	406.9	126	-3.1	1.64	18.42	-4.2	-46	70
DAY 8 (DB).22H PST	126	406.9	24.16	407.0	349	458	407.0	126	-1.0	1.64	18.34	-1.1	-62	58
DAY 15 (DB)	9	418.9	22.86	413.0	394	458	416.2	9	3.6	6.62	19.87	-3.1	-19	41
DAY 15 (DB).PRE-DS	116	404.3	23.13	407.5	336	456	406.1	116	-1.9	1.58	16.15	-0.5	-56	36
DAY 15 (DB).1-2H PST	117	401.9	23.14	400.0	344	468	406.5	117	-4.6	1.67	18.10	-3.7	-54	40
DAY 15 (DB).4H PST	118	401.5	23.15	402.0	339	463	405.4	118	-3.8	1.69	18.40	0.4	-63	44
DAY 29 (DB)	106	408.1	23.69	406.0	361	461	407.6	106	0.4	1.82	18.35	-1.0	-37	65
DAY 36 (DB).PRE-DS	79	406.3	25.88	406.0	345	484	407.4	79	0.9	2.35	20.88	3.3	-42	58
DAY 36 (DB).1-2H PST	76	406.1	25.14	407.0	339	471	407.5	76	-1.3	2.37	20.62	-1.0	-43	72
DAY 36 (DB).4H PST	78	404.6	24.72	406.5	347	470	407.4	78	-1.9	2.34	19.82	-0.7	-48	72
DAY 43 (DB)	88	406.6	23.84	406.5	330	473	407.3	88	-0.7	1.76	16.38	-1.5	-34	61
MAXIMUM VALUE (DB)	128	428.1	21.34	429.0	362	486	407.0	128	21.1	1.47	16.68	20.1	-25	73
END POINT (DB)	128	406.9	23.65	407.5	330	473	407.0	128	-0.1	1.72	19.69	-0.8	-48	65
BASE (OPEN)	128	406.9	23.35	406.0	330	473	407.0	128	-0.1	1.74	19.70	-1.0	-48	65
DAY 4 (OPEN)	123	411.6	21.91	413.0	352	464	407.1	123	6.6	1.46	16.23	7.3	-28	66
WEEK 1 (OPEN)	121	411.2	22.35	413.0	345	462	407.0	121	6.2	1.65	18.26	5.0	-61	64
WEEK 2 (OPEN)	120	409.7	20.42	410.5	351	460	406.9	120	3.8	1.48	16.22	3.1	-58	41
WEEK 4 (OPEN)	125	407.8	19.67	407.0	365	451	406.9	125	1.0	1.70	19.05	0.7	-58	77
WEEK 8 (OPEN)	124	408.0	21.65	404.0	341	472	406.6	124	1.4	1.62	18.09	1.2	-41	51
WEEK 16 (OPEN)	119	407.2	23.62	409.0	348	474	407.1	119	0.7	1.72	18.80	1.1	-52	48
WEEK 24 (OPEN)	78	408.9	21.15	410.0	350	461	401.8	78	6.8	2.15	18.73	8.7	-54	48
WEEK 40 (OPEN)	16	411.7	23.10	420.0	370	444	405.5	15	6.1	4.52	18.10	6.1	-32	38
WEEK 52 (OPEN)	2	421.5	10.61	421.5	424	439	392.8	2	28.7	14.00	19.80	28.7	15	53
MAXIMUM VALUE (OPEN)	128	428.7	17.97	429.0	386	474	407.0	128	21.7	1.32	14.94	21.0	-15	77
END POINT (OPEN)	128	409.5	22.74	411.0	356	474	407.0	128	3.5	1.82	20.66	3.0	-54	53
Pall/Pall <3 months														
BASELINE (DB)	178	410.7	21.80	413.0	352	466								
AVERAGE PREDOSE	178	414.1	21.50	416.0	359	471								
DAY 4 (DB).4H PST	174	415.2	20.90	420.0	364	472	414.2	174	5.0	1.27	16.73	5.0	-42	69
DAY 4 (DB).10H PST	171	415.6	21.92	420.0	369	502	413.6	171	5.8	1.38	18.11	5.7	-51	72
DAY 4 (DB).22H PST	171	415.9	23.61	421.0	362	482	414.7	171	5.2	1.42	18.53	4.7	-66	52
DAY 8 (DB).4H PST	174	418.0	19.32	418.0	360	471	414.2	174	3.7	1.35	16.43	3.5	-46	62
DAY 8 (DB).10H PST	171	417.5	22.38	418.0	345	483	414.1	171	3.3	1.50	19.73	3.5	-72	60
DAY 8 (DB).22H PST	176	415.1	23.12	417.0	362	490	413.9	176	5.3	1.52	20.12	6.0	-29	65

Pali/Pali <=1 months														
DAY 15 (ES)	24	428.4	21.97	427.0	122	466	429.7	24	-1.3	2.92	18.34	-1.2	-35	59
DAY 15 (ES),PRE-DS	161	411.7	22.06	413.0	156	458	413.7	162	0.1	1.42	17.45	-0.2	-46	74
DAY 15 (ES),1-2H PST	160	412.4	19.80	411.5	162	463	411.5	160	0.9	1.44	17.63	1.2	-65	53
DAY 15 (ES),4H PST	146	414.1	18.17	414.0	166	462	412.0	142	1.1	1.34	16.32	1.3	-42	57
DAY 19 (ES)	160	416.1	20.95	416.5	157	467	416.1	160	1.0	1.46	17.54	1.0	-41	48
DAY 36 (ES),PRE-DS	103	416.2	22.02	416.0	152	475	413.4	100	1.8	1.86	18.86	3.7	-46	41
DAY 36 (ES),1-2H PST	106	412.2	20.61	410.0	152	476	412.8	104	-1.7	1.57	16.18	-1.6	-46	36
DAY 36 (ES),4H PST	104	416.2	20.68	414.0	171	481	413.5	104	1.8	1.76	17.96	-0.2	-35	63
DAY 43 (ES)	126	416.2	21.71	416.0	164	471	416.4	135	-0.2	1.36	16.13	-0.7	-36	42
MAXIMUM VALUE (ES)	178	427.2	20.33	427.0	182	502	414.1	178	23.7	1.10	14.71	23.6	-14	78
END POINT (ES)	178	414.1	21.84	414.0	152	471	414.1	178	-0.1	1.38	17.02	-0.7	-42	58
BASE (OPEN)	178	414.2	21.96	414.5	152	471	414.1	178	0.1	1.36	16.85	-0.6	-42	58
DAY 4 (OPEN)	164	416.2	24.30	416.0	164	498	414.5	164	0.7	1.60	18.68	0.6	-42	47
WEEK 1 (OPEN)	161	414.0	20.42	416.0	164	466	413.8	161	0.2	1.18	14.40	-1.0	-42	40
WEEK 2 (OPEN)	136	414.8	22.62	416.5	162	468	414.8	136	0.1	1.76	20.43	0.2	-42	64
WEEK 4 (OPEN)	73	414.5	21.54	416.0	162	467	416.2	72	-0.9	1.56	16.58	-1.6	-36	17
WEEK 8 (OPEN)	11	401.2	28.60	400.5	379	442	410.5	12	-9.1	6.60	19.40	-4.6	-38	14
WEEK 16 (OPEN)	1	417.0	14.79	399.0	196	467	414.4	2	3.6	13.99	24.62	-5.0	-36	40
WEEK 24 (OPEN)	1	417.0	1.41	417.0	416	418	413.2	2	3.7	10.34	14.62	3.7	-7	14
MAXIMUM VALUE (OPEN)	173	426.9	21.61	424.0	162	490	412.9	173	11.0	1.30	16.75	11.0	-22	64
END POINT (OPEN)	173	416.1	21.02	416.0	152	471	413.9	173	1.2	1.42	18.69	1.1	-42	64
Pali/Pali >1 months														
BASELINE (ES)	504	409.2	23.18	410.0	137	477								
AVERAGE REDUCE	504	412.6	20.65	411.8	156	476								
DAY 4 (ES),4H PST	450	417.1	20.80	416.0	153	474	412.5	450	4.6	0.75	16.53	4.1	-41	52
DAY 4 (ES),10H PST	481	416.0	20.32	414.8	152	469	412.6	481	3.4	0.62	17.12	3.3	-103	44
DAY 4 (ES),22H PST	479	419.8	21.11	419.8	142	467	412.6	479	6.4	0.82	17.85	6.3	-49	64
DAY 8 (ES),4H PST	459	416.4	20.58	416.0	136	476	412.6	459	3.8	0.81	18.81	4.2	-42	52
DAY 8 (ES),10H PST	496	416.1	20.35	416.0	142	478	412.5	494	3.8	0.81	18.11	3.7	-62	55
DAY 8 (ES),22H PST	496	417.5	22.64	417.0	146	482	412.5	495	5.1	0.85	18.92	5.0	-62	71
DAY 15 (ES)	34	424.6	26.61	426.0	180	471	423.7	34	0.1	2.42	19.97	1.8	-37	47
DAY 15 (ES),PRE-DS	468	412.9	22.02	413.0	140	483	411.7	467	1.1	0.84	17.92	1.1	-62	47
DAY 15 (ES),1-2H PST	467	410.7	21.08	411.0	157	474	411.8	466	-1.1	0.89	19.07	-1.0	-78	55
DAY 15 (ES),4H PST	467	411.6	21.93	414.5	112	483	411.6	466	1.8	0.91	19.43	1.5	-104	48
DAY 19 (ES)	473	412.7	21.89	413.0	137	496	412.8	472	-0.2	0.86	18.69	1.6	-62	74
DAY 36 (ES),PRE-DS	393	411.1	21.66	413.0	142	512	411.8	391	-0.8	0.94	18.86	-0.1	-77	63
DAY 36 (ES),1-2H PST	391	409.2	22.32	408.0	140	481	411.7	390	-1.6	1.02	20.35	-1.6	-95	72
DAY 36 (ES),4H PST	285	410.6	20.61	411.0	151	474	411.2	284	-0.7	0.97	19.07	0.3	-90	45
DAY 43 (ES)	429	411.5	21.92	411.0	151	506	412.6	429	-1.0	0.92	18.34	-0.1	-71	77
MAXIMUM VALUE (ES)	506	436.6	18.67	437.0	306	522	412.6	504	23.9	0.65	14.69	23.7	-17	77
END POINT (ES)	506	412.2	22.35	413.0	151	506	412.6	504	-0.4	0.86	19.39	0.0	-71	77
BASE (OPEN)	506	412.1	22.38	413.0	151	506	412.6	504	-0.5	0.85	19.37	0.0	-71	77
DAY 4 (OPEN)	476	412.4	21.84	413.0	151	498	412.6	474	-0.1	0.84	18.38	0.5	-64	62
WEEK 1 (OPEN)	486	411.6	21.94	410.0	152	488	412.6	485	-0.9	0.87	18.37	-0.1	-69	55
WEEK 2 (OPEN)	483	412.1	20.58	411.0	149	472	412.7	481	-0.6	0.84	18.45	-1.7	-66	55
WEEK 4 (OPEN)	493	410.7	21.85	411.0	121	478	412.8	492	-2.1	0.85	18.88	-0.6	-77	67
WEEK 8 (OPEN)	473	410.0	21.41	410.0	149	467	412.6	470	-2.6	0.88	19.06	-2.1	-69	59
WEEK 16 (OPEN)	374	411.0	20.63	414.0	159	478	412.7	372	0.3	1.06	20.33	0.3	-72	70
WEEK 24 (OPEN)	247	412.6	22.37	414.0	154	488	412.6	247	0.3	1.32	20.33	-0.6	-67	69
WEEK 40 (OPEN)	50	411.7	18.02	411.0	176	442	409.4	50	2.3	2.47	17.43	3.0	-29	49
WEEK 52 (OPEN)	6	422.4	6.62	426.0	411	439	408.4	6	14.0	8.54	20.90	13.7	-11	42
MAXIMUM VALUE (OPEN)	504	428.2	21.04	429.0	178	535	412.6	502	16.1	0.80	17.92	16.0	-36	170
END POINT (OPEN)	504	412.2	21.73	411.5	150	479	412.6	502	-0.1	0.91	19.33	0.0	-69	70
Olan/Pali <=1 months														
BASELINE (ES)	106	407.2	21.27	407.0	144	464								
AVERAGE REDUCE	106	411.0	18.47	409.2	147	462								
DAY 4 (ES),4H PST	104	409.1	22.34	411.5	152	465	410.9	104	-1.8	1.64	16.94	-1.6	-37	35
DAY 4 (ES),10H PST	103	410.0	21.52	410.0	148	462	410.9	102	-0.8	1.62	16.64	-0.1	-48	42
DAY 4 (ES),22H PST	98	408.9	23.42	407.0	148	465	409.9	98	-0.9	1.62	16.19	-2.1	-59	32
DAY 8 (ES),4H PST	103	412.3	22.70	411.0	142	462	410.6	103	1.6	1.80	18.16	1.3	-34	57
DAY 8 (ES),10H PST	103	412.0	21.62	414.0	154	466	410.6	102	1.4	1.63	17.07	1.2	-40	53
DAY 8 (ES),22H PST	100	414.0	23.50	411.0	154	480	410.4	100	3.6	1.82	18.17	1.4	-42	52
DAY 15 (ES),PRE-DS	106	410.2	22.33	409.0	162	476	411.1	105	-0.9	1.74	17.82	-0.1	-42	52
DAY 15 (ES),1-2H PST	99	411.1	22.38	410.0	157	466	410.2	99	1.0	1.87	19.65	1.7	-33	54
DAY 15 (ES),4H PST	99	412.9	21.06	413.0	156	469	410.4	99	1.4	1.86	18.62	1.1	-38	53
DAY 19 (ES)	89	414.4	20.71	416.0	157	464	410.7	92	1.7	1.79	16.83	1.7	-39	51
DAY 36 (ES),PRE-DS	73	410.2	21.61	413.0	156	467	409.6	72	1.4	1.86	15.92	1.7	-36	42
DAY 36 (ES),1-2H PST	76	409.6	20.51	409.5	156	457	409.7	76	0.1	2.04	17.76	1.6	-41	50
DAY 36 (ES),4H PST	74	412.7	22.08	415.0	161	473	409.2	74	1.6	2.34	20.13	0.3	-46	52
DAY 43 (ES)	71	411.6	21.35	413.0	165	468	410.2	71	1.4	1.82	15.46	1.3	-21	37
MAXIMUM VALUE (ES)	106	424.6	21.17	425.0	178	480	411.0	106	23.5	1.44	14.86	21.3	-12	61
END POINT (ES)	106	411.2	21.79	408.5	157	464	411.0	106	0.1	1.86	16.06	-0.1	-32	41
BASE (OPEN)	106	409.2	21.86	408.5	157	464	411.0	106	-1.8	1.61	16.62	-0.1	-42	41
DAY 4 (OPEN)	88	416.6	21.06	417.0	156	462	409.6	88	6.7	2.12	19.91	7.0	-61	61
WEEK 1 (OPEN)	90	417.2	20.63	416.5	161	462	411.7	90	5.6	1.95	18.46	7.2	-46	48
WEEK 2 (OPEN)	77	411.2	19.92	415.0	172	464	410.2	77	1.9	1.68	13.83	1.1	-27	36
WEEK 4 (OPEN)	66	406.7	20.72	406.0	169	462	410.6	66	-3.8	2.35	16.65	-5.0	-42	43
WEEK 8 (OPEN)	22	410.9	18.48	417.5	165	448	411.2	22	-0.3	3.69	16.88	0.5	-27	30
WEEK 16 (OPEN)	1	379.0		379.0	379	379	416.2	1	-37.1			-17.1	-37	-37
MAXIMUM VALUE (OPEN)	103	424.6	20.33	426.0	155	469	410.2	103	14.1	1.68	17.10	14.0	-48	61
END POINT (OPEN)	103	410.1	22.67	408.0	155	468	410.2	103	-0.2	1.70	17.39	0.0	-48	48

Olan/Pali >1 mo/ba														
BASELINE (DB)	143	406.4	23.61	406.0	332	473								
AVERAGE REDUCE	143	409.9	20.54	408.0	345	474								
DAY 4 (DB),4H PST	136	406.9	22.62	406.5	343	476	408.5	136	-1.6	1.64	17.97	-1.2	-52	51
DAY 4 (DB),10H PST	136	409.2	21.86	408.5	358	468	409.2	136	0.0	1.69	19.65	0.2	-62	60
DAY 4 (DB),22H PST	136	409.0	23.00	410.0	356	462	408.5	136	0.5	1.44	16.75	0.0	-45	40
DAY 8 (DB),4H PST	128	408.6	19.82	409.0	362	461	408.9	128	-0.3	1.55	18.15	-1.0	-52	47
DAY 8 (DB),10H PST	127	410.6	21.74	411.0	352	465	408.2	127	1.7	1.66	19.33	0.7	-49	55
DAY 8 (DB),22H PST	141	410.0	23.69	406.0	358	472	408.2	141	1.1	1.76	20.83	1.0	-42	64
DAY 15 (DB),PRE-DS	140	409.6	22.07	410.0	354	465	409.0	140	0.7	1.42	16.96	0.6	-44	51
DAY 15 (DB),1-2H PST	139	408.2	23.16	410.0	348	459	409.0	139	-0.8	1.76	20.73	-1.1	-49	68
DAY 15 (DB),4H PST	138	410.8	22.36	411.5	350	466	408.9	138	1.8	1.65	19.38	1.6	-42	67
DAY 29 (DB)	126	412.8	24.03	417.0	332	473	409.2	126	3.6	1.92	21.54	3.8	-51	66
DAY 36 (DB),PRE-DS	119	408.3	23.93	411.0	350	462	409.0	119	-0.7	1.90	20.75	-0.7	-60	49
DAY 36 (DB),1-2H PST	120	409.9	25.02	409.5	354	475	409.2	120	0.6	1.86	20.33	1.2	-55	55
DAY 36 (DB),4H PST	118	411.4	23.78	411.0	361	468	409.1	118	3.3	1.85	20.16	3.6	-55	56
DAY 43 (DB)	123	406.1	23.33	406.5	348	470	409.0	122	-3.0	1.72	17.95	-4.2	-62	29
MAXIMUM VALUE (DB)	143	422.2	18.77	421.0	378	478	409.0	143	23.3	1.35	16.11	23.7	-26	68
END POINT (DB)	143	407.0	22.86	409.0	342	478	409.0	143	-3.0	1.61	19.04	-3.0	-62	38
BASE (OPEN)	143	407.0	23.52	409.0	342	478	409.0	143	-3.1	1.61	18.94	-3.0	-62	38
DAY 4 (OPEN)	134	416.5	21.32	416.0	352	476	409.2	134	6.3	1.62	18.75	7.0	-62	52
WEEK 1 (OPEN)	134	416.0	21.34	416.5	364	468	407.9	134	7.1	1.46	16.80	6.7	-33	48
WEEK 2 (OPEN)	132	410.2	22.58	411.5	348	461	408.7	132	1.6	1.64	18.83	1.6	-61	56
WEEK 4 (OPEN)	139	409.0	21.86	406.0	362	466	408.8	139	0.1	1.62	19.36	3.1	-58	49
WEEK 8 (OPEN)	128	409.4	22.78	411.0	348	478	409.2	128	0.3	1.69	19.64	3.6	-55	62
WEEK 16 (OPEN)	128	408.8	22.82	406.0	364	476	409.2	126	-0.3	1.86	20.66	-0.3	-29	73
WEEK 24 (OPEN)	84	406.2	25.11	406.5	346	466	406.1	84	0.2	2.16	19.83	0.7	-57	39
WEEK 40 (OPEN)	16	396.9	31.16	396.5	337	443	398.3	16	-1.4	7.96	31.83	3.1	-41	32
MAXIMUM VALUE (OPEN)	143	428.7	18.82	426.0	371	478	409.0	143	19.7	1.35	16.14	20.1	-26	73
END POINT (OPEN)	143	409.7	23.72	414.0	337	476	409.0	143	0.7	1.69	20.22	1.7	-29	73

B. QTc Fridericia Results The following are selected sections of the sponsor's summary table (as above) on QTc Fridericia results for selected treatment groups. OL Pal treatment failed to show remarkable group mean changes in QTc Fridericia following DB Pal treatment (for assessment weeks that had at least 50 subjects which included up to a 24 week assessment time-point in some subgroups). However, these OL trials have several major study design limitations that may lead to failure to reveal a clear drug effect on QTc interval (e.g. considerations on potential subject variance on timing of assessments and dosing, among other limitations as previously noted).

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output [OPEN3]. ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Data	Change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max

Pali/Pali <=1 months														
BASELINE (DB)	176	395.1	20.02	356.0	342	465								
AVERAGE PERIOD	176	397.6	19.99	357.2	354	465								
DAY 4 (DB),4H PST	174	395.9	20.12	356.0	350	460	397.6	174	-1.8	1.01	12.39	-1.1	-49	39
DAY 4 (DB),10H PST	171	397.1	20.03	357.0	357	467	397.6	171	-0.6	1.12	14.63	-0.7	-70	66
DAY 4 (DB),22H PST	171	399.1	20.37	358.0	357	461	397.8	171	1.2	1.15	14.98	1.7	-62	62
DAY 8 (DB),4H PST	174	396.2	19.11	354.5	340	454	397.8	174	-1.4	1.06	14.04	-1.1	-56	44
DAY 8 (DB),10H PST	173	396.0	19.66	354.0	332	459	398.0	172	-1.1	1.12	16.13	-1.1	-71	46
DAY 8 (DB),22H PST	176	399.4	19.84	357.0	344	463	397.6	176	1.8	1.12	16.35	1.7	-61	63
DAY 15 (DB)	34	415.1	19.32	411.5	381	456	414.1	34	1.0	2.16	15.60	0.4	-32	43
DAY 15 (DB),PRE-DS	162	394.1	19.03	353.5	354	439	394.9	162	-0.8	1.14	14.08	-0.7	-45	29
DAY 15 (DB),1-2H PST	160	392.2	17.88	359.0	352	439	394.7	160	-2.5	1.15	14.09	-3.0	-72	43
DAY 15 (DB),4H PST	148	392.7	17.92	353.0	357	442	395.1	148	-3.4	1.08	13.17	-1.1	-69	31
DAY 29 (DB)	160	399.5	19.73	358.5	351	464	398.4	160	1.1	1.12	13.89	0.0	-31	33
DAY 36 (DB),PRE-DS	103	399.7	19.32	359.0	356	465	396.2	103	3.4	1.39	14.11	3.7	-26	40
DAY 36 (DB),1-2H PST	106	396.5	18.33	363.0	358	462	397.2	106	-1.8	1.12	11.68	-1.6	-38	30
DAY 36 (DB),4H PST	104	397.2	18.36	356.5	366	463	397.1	104	0.2	1.12	11.62	-0.6	-25	37
DAY 43 (DB)	126	401.9	20.30	399.0	358	464	400.1	126	1.6	1.14	12.72	1.1	-28	36
MAXIMUM VALUE (DB)	176	413.7	19.97	411.0	376	467	397.6	176	16.1	0.91	12.00	15.7	-12	63
END POINT (DB)	176	398.4	18.91	357.0	359	464	397.6	176	0.8	1.08	13.33	0.3	-30	43
BASE (OPEN)	176	398.5	18.96	357.0	358	464	397.6	176	0.9	0.99	13.16	0.6	-32	43
DAY 4 (OPEN)	164	398.2	21.43	398.5	337	472	399.5	164	-0.1	1.30	14.91	-0.6	-39	32
WEEK 1 (OPEN)	161	397.3	18.43	354.0	354	467	397.4	161	-0.1	1.04	13.16	1.1	-34	34
WEEK 2 (OPEN)	136	396.8	20.40	396.0	357	468	398.8	136	-1.1	1.16	15.82	-0.7	-68	37
WEEK 4 (OPEN)	73	396.4	16.77	396.5	356	434	397.1	73	-0.8	1.64	13.80	-0.6	-32	33
WEEK 8 (OPEN)	33	398.3	19.82	387.0	367	432	394.6	33	-4.1	4.34	14.68	-4.6	-32	19
WEEK 16 (OPEN)	3	395.0	10.41	380.0	376	408	395.6	3	1.4	14.62	15.14	0.1	-32	19
WEEK 24 (OPEN)	1	394.0	4.34	394.0	391	397	398.2	1	-4.2	16.68	12.33	-4.2	-21	12
MAXIMUM VALUE (OPEN)	173	406.2	19.30	407.0	362	472	397.6	173	8.7	0.94	12.30	8.0	-20	36
END POINT (OPEN)	173	398.4	18.41	356.0	356	468	397.6	173	0.9	1.07	14.04	1.0	-69	37
Pali/Pali >1 months														
BASELINE (DB)	504	395.5	19.42	356.0	337	470								
AVERAGE PERIOD	504	398.2	18.38	397.1	355	465								
DAY 4 (DB),4H PST	490	395.6	17.47	354.0	357	462	398.1	490	-1.6	0.86	12.48	-1.7	-61	33
DAY 4 (DB),10H PST	481	395.6	18.15	354.0	337	463	398.1	481	-1.6	0.82	13.80	-1.7	-74	44
DAY 4 (DB),22H PST	479	401.0	18.39	401.0	346	466	398.1	479	1.9	0.80	13.30	3.7	-37	40
DAY 8 (DB),4H PST	499	396.4	18.09	356.0	342	460	398.1	498	-1.6	0.82	14.08	-0.7	-58	51
DAY 8 (DB),10H PST	496	397.0	18.08	356.0	357	462	397.9	494	-0.9	0.82	13.68	0.0	-52	42
DAY 8 (DB),22H PST	496	401.5	18.31	400.0	346	461	398.0	496	3.6	0.83	14.08	4.0	-44	43
DAY 15 (DB)	14	409.9	24.04	411.5	367	460	411.2	14	-1.3	2.64	15.41	-1.0	-25	30
DAY 15 (DB),PRE-DS	464	397.8	18.65	357.0	350	470	397.4	467	0.7	0.82	13.34	1.0	-60	37
DAY 15 (DB),1-2H PST	467	393.1	17.75	351.0	350	469	397.1	466	-4.0	0.81	12.98	-4.0	-62	38
DAY 15 (DB),4H PST	467	394.2	17.31	356.0	332	443	396.9	466	-1.6	0.86	14.15	-1.7	-72	40
DAY 29 (DB)	473	398.2	18.67	358.0	350	491	398.4	472	-0.1	0.84	13.54	0.7	-49	45
DAY 36 (DB),PRE-DS	293	398.4	17.62	358.0	357	446	396.9	291	1.5	0.75	14.84	1.7	-42	42
DAY 36 (DB),1-2H PST	291	395.1	17.77	354.0	345	457	396.9	290	-1.8	0.76	14.52	-1.3	-46	50
DAY 36 (DB),4H PST	285	395.9	16.57	356.0	352	462	396.4	284	-0.7	0.72	14.11	-0.7	-57	35
DAY 43 (DB)	429	398.2	19.40	397.0	344	502	398.8	429	0.8	0.71	14.72	1.0	-51	60
MAXIMUM VALUE (DB)	504	414.6	23.98	414.0	372	502	398.2	504	16.5	0.82	11.66	16.0	-19	69
END POINT (DB)	504	395.0	19.69	356.0	344	502	398.2	504	0.8	0.85	14.69	1.2	-51	69
BASE (OPEN)	476	395.2	19.80	356.0	344	502	398.2	504	1.0	0.85	14.64	1.1	-51	69
DAY 4 (OPEN)	475	398.0	18.52	397.0	342	483	398.8	474	0.1	0.82	13.48	-0.7	-44	39
WEEK 1 (OPEN)	486	397.2	18.89	356.0	348	468	398.1	485	-0.8	0.85	14.33	0.0	-52	48
WEEK 2 (OPEN)	483	398.1	18.64	357.0	345	486	398.2	480	-0.2	0.87	14.80	-0.7	-52	55
WEEK 4 (OPEN)	493	397.2	19.06	357.0	316	465	398.3	492	-1.2	0.89	15.06	-0.1	-79	41
WEEK 8 (OPEN)	471	396.2	17.82	356.0	354	459	398.8	470	-1.8	0.88	14.84	-1.0	-62	41
WEEK 16 (OPEN)	374	398.5	18.32	359.0	352	460	397.7	373	0.7	0.76	14.65	0.7	-50	41
WEEK 24 (OPEN)	347	398.8	18.60	358.0	348	464	397.8	347	1.5	0.94	14.86	1.0	-44	38
WEEK 40 (OPEN)	50	395.8	15.54	396.0	365	447	395.8	50	-0.0	1.70	12.01	-0.7	-24	30
WEEK 52 (OPEN)	5	414.2	18.88	419.0	397	423	400.2	5	13.5	6.52	15.68	13.7	-2	34
MAXIMUM VALUE (OPEN)	504	411.1	19.60	410.0	364	579	398.1	503	11.0	0.83	13.59	11.0	-22	117
END POINT (OPEN)	504	398.4	18.48	356.0	344	462	398.1	503	0.6	0.86	14.51	0.7	-62	61
Olan/Pali <=1 months														
BASELINE (DB)	106	391.0	17.65	393.5	342	429								
AVERAGE PERIOD	106	391.1	15.10	396.8	351	436								
DAY 4 (DB),4H PST	104	391.9	17.33	393.0	349	437	395.1	104	-3.1	1.09	11.01	-3.8	-29	31
DAY 4 (DB),10H PST	103	392.2	18.32	393.0	341	442	395.0	103	-3.7	1.19	12.02	-3.1	-35	33
DAY 4 (DB),22H PST	96	394.4	19.07	396.0	362	439	394.7	98	-0.2	1.31	12.98	-0.6	-37	39
DAY 8 (DB),4H PST	103	391.8	18.09	396.0	356	446	395.1	102	-3.1	1.16	12.77	-3.7	-35	44
DAY 8 (DB),10H PST	103	391.8	17.41	396.0	344	437	394.9	102	-3.2	1.10	12.08	-3.0	-26	35
DAY 8 (DB),22H PST	100	398.7	18.08	398.0	342	467	394.6	100	3.9	1.48	14.77	3.3	-28	58
DAY 15 (DB),PRE-DS	106	396.1	17.65	396.0	356	466	395.1	106	-0.0	1.18	12.69	0.7	-38	43
DAY 15 (DB),1-2H PST	99	392.2	19.08	393.0	346	446	394.5	99	-3.2	1.34	13.22	-3.8	-37	39
DAY 15 (DB),4H PST	99	392.9	18.34	396.0	356	461	394.8	99	-1.9	1.36	12.43	-1.7	-38	33
DAY 29 (DB)	89	396.2	17.58	396.0	349	429	395.1	89	1.1	1.37	12.54	0.0	-22	34
DAY 36 (DB),PRE-DS	73	396.7	17.82	396.0	342	441	394.8	73	1.7	1.55	13.36	1.0	-26	34
DAY 36 (DB),1-2H PST	76	394.6	17.63	394.0	352	446	394.6	76	-0.1	1.55	13.54	-0.1	-28	33
DAY 36 (DB),4H PST	74	395.4	18.14	396.0	359	448	394.4	74	1.1	1.64	14.13	1.0	-34	47
DAY 43 (DB)	71	396.7	17.12	397.0	340	429	394.6	71	1.1	1.56	13.13	0.0	-23	36
MAXIMUM VALUE (DB)	106	411.5	18.33	410.5	372	467	395.1	106	16.4	1.32	12.59	15.0	-10	59
END POINT (DB)	106	395.7	18.45	394.5	346	448	395.1	106	0.7	1.37	13.06	-0.1	-31	34
BASE (OPEN)	106	394.8	18.48	393.0	346	449	395.1	106	-0.1	1.32	13.63	-1.0	-32	36
DAY 4 (OPEN)	98	391.9	17.22	391.5	356	432	393.5	98	-1.6	1.55	14.50	-0.6	-66	28
WEEK 1 (OPEN)	90	396.0	17.67	396.0	352	440	396.2	90	-0.2	1.38	13.34	0.2	-44	39
WEEK 2 (OPEN)	77	391.4	15.73	394.0	359	439	394.7	77	-1.1	1.12	9.82	-1.1	-20	32
WEEK 4 (OPEN)	66	392.1	17.09	390.0	352	436	394.2	66	-2.2	1.65	12.31	-3.1	-22	39
WEEK 8 (OPEN)	22	392.6	13.97	393.0	364	416	395.8	22	-2.2	2.01	9.45	-3.1	-17	15
WEEK 16 (OPEN)	1	376.0		376.0	376	376	393.2	1	-18.1			-18.1	-18	-18
MAXIMUM VALUE (OPEN)	103	401.7	17.41	403.0	358	441	394.4	103	6.5	1.34	12.54	7.7	-44	32
END POINT (OPEN)	103	391.6	17.52	391.0	356	441	394.4	103	-0.7	1.39	12.85	-0.7	-44	39

Class/Pali >1 months														
BASELINE (ZH)	143	391.6	19.63	354.0	333	432								
AVERAGE PERIOD3H	143	391.0	16.58	353.0	348	444								
DAY 4 (ZH).4H PST	116	389.8	18.61	389.0	344	448	392.6	116	-1.7	1.18	12.72	-3.8	-36	16
DAY 4 (ZH).10H PST	116	391.2	19.48	391.0	354	441	393.4	116	-2.2	1.39	13.89	-1.2	-34	16
DAY 4 (ZH).22H PST	116	394.2	19.13	394.0	352	440	392.5	115	1.7	0.86	11.34	1.6	-40	12
DAY 8 (ZH).4H PST	118	391.1	16.76	391.0	348	432	392.9	118	-1.8	1.01	11.87	-0.7	-37	12
DAY 8 (ZH).10H PST	117	392.8	17.97	393.0	344	438	392.9	117	-0.0	1.12	12.14	-0.6	-42	12
DAY 8 (ZH).22H PST	141	394.6	19.45	394.0	347	442	392.9	141	1.7	1.36	14.54	0.1	-52	46
DAY 15 (ZH).PRE-DS	140	394.4	19.11	395.5	342	449	393.0	140	1.4	1.09	12.92	1.1	-22	12
DAY 15 (ZH).1-2H PST	119	389.8	18.58	388.0	339	438	391.0	119	-1.1	1.11	12.06	-1.0	-37	30
DAY 15 (ZH).4H PST	118	391.8	19.18	393.0	345	447	392.9	118	-1.1	1.02	12.11	0.5	-32	28
DAY 29 (ZH)	126	394.2	20.12	397.5	336	442	393.5	125	0.9	1.26	15.14	1.2	-52	40
DAY 36 (ZH).PRE-DS	119	394.4	19.17	393.0	351	446	393.2	119	1.2	1.17	12.82	1.8	-37	16
DAY 36 (ZH).1-2H PST	120	394.8	20.18	394.5	350	440	393.6	120	1.2	1.38	14.84	1.6	-45	24
DAY 36 (ZH).4H PST	118	396.0	19.79	396.0	352	442	393.5	118	1.6	1.16	12.64	3.0	-40	28
DAY 43 (ZH)	123	392.7	20.06	391.0	346	446	393.4	122	-0.7	1.32	14.61	-0.1	-67	28
MAXIMUM VALUE (ZH)	143	410.0	19.39	408.0	368	448	393.0	143	17.0	0.97	11.65	16.7	-24	46
END POINT (ZH)	143	392.2	19.77	393.0	346	446	393.0	143	-0.7	1.32	14.67	-0.1	-67	28
BASE (QTSEN)	143	392.6	19.81	393.0	346	446	393.0	143	-0.6	1.32	14.72	-0.1	-67	28
DAY 4 (QTSEN)	134	391.0	17.66	391.5	342	446	393.2	134	-0.1	1.11	12.86	1.8	-38	26
WEEK 1 (QTSEN)	134	394.4	18.38	394.0	346	441	392.1	134	3.1	1.06	12.31	3.4	-42	28
WEEK 2 (QTSEN)	131	392.6	17.83	393.0	348	432	392.8	132	-0.6	1.18	13.56	-0.2	-38	26
WEEK 4 (QTSEN)	139	392.1	17.68	393.0	355	441	393.6	138	-0.8	1.18	15.30	-1.3	-51	28
WEEK 8 (QTSEN)	138	392.6	17.92	393.0	352	441	392.8	138	-0.1	1.30	14.10	0.2	-46	34
WEEK 16 (QTSEN)	134	392.7	19.63	393.0	356	443	393.2	134	-0.6	1.35	15.02	-0.8	-61	58
WEEK 24 (QTSEN)	84	392.6	19.64	393.5	348	432	390.8	84	1.7	1.52	13.91	3.7	-36	38
WEEK 40 (QTSEN)	16	396.2	20.73	388.5	367	428	383.1	16	3.1	2.72	10.87	3.8	-20	22
MAXIMUM VALUE (QTSEN)	143	406.8	16.48	406.0	366	462	393.0	143	13.8	1.02	12.22	13.7	-30	58
END POINT (QTSEN)	143	394.0	19.76	393.0	347	462	393.0	143	1.0	1.18	15.30	1.7	-61	58

QTc linear derived and linear sagie interval results were generally clinically unremarkable during OL Pal treatment for assessment weeks that had at least up to 50 subjects who were assessed which included assessments for up to 24 weeks of OL treatment in subgroups.

Results of Ongoing Trials -301 and -701
Results from these ongoing trials are not provided in the original submission since they are ongoing with blinded data.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Refer to Table series 10.2 in the appendix of this review for criteria used for outlier ECG values.

Results of Short-Term Phase III Trials (-303, -34, -305).
Reviewer Comment. *The following comments are based on numerical comparisons between treatment groups of results provided in summary tables found in the SCS or in the SCS appendices (results of statistical group comparisons could not be found in these summary tables).*

A Greater Incidence in High Heart Rate Outliers in Pal Groups compared to the Placebo Group.
The sponsor's results below (as provided in the SCS) show numerically greater incidence of outliers for high heart rate in Pal groups compared to the placebo group.

Greater Incidence in High PR Interval Outliers in Some Pal Groups compared to the Placebo Group
High PR interval outlier results show inconsistently greater incidence among Pal groups compared to the placebo group (based on numerical comparisons). Since this observation appears to be inconsistent among Pal groups and does not appear to increase with increasing dose-level, then these results, alone do not provide sufficient evidence for a drug effect on PR

prolongation. However, a small mean increase in PR interval (compared to pre-dose values) was observed in Phase III trials, as previously described under the preceding section of this review.

Clinically Unremarkable QRS and QTraw Interval Results. *Results on QRS and QTraw interval outliers is unremarkable.*

Table 85: Number of Subjects With Treatment-Emergent Abnormal ECG Values During the Double-Blind Period (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
Heart rate	350	124	232	243	238	113	950	357
Abnormally high	79 (23)	39 (31)	77 (33)	92 (38)	99 (42)	33 (29)	340 (36)	111 (31)
Abnormally low	29 (8)	6 (5)	4 (2)	10 (4)	13 (5)	2 (2)	35 (4)	22 (6)
PR interval	350	124	232	243	238	113	950	357
Abnormally high	6 (2)	7 (6)	4 (2)	5 (2)	6 (3)	6 (5)	28 (3)	7 (2)
Abnormally low	0	0	0	0	0	0	0	0
QRS interval	350	124	232	243	238	113	950	357
Abnormally high	2 (1)	0	0	1 (<1)	0	1 (1)	2 (<1)	3 (1)
Abnormally low	0	0	0	0	0	0	0	0
QT interval	350	124	232	243	238	113	950	357
Abnormally high	0	0	0	0	0	0	0	0
Abnormally low	0	0	0	0	0	0	0	0

Note: Percentages calculated with the number of subjects per parameter as denominator.
Note: Heart rate: abnormally low: <=50 bpm, abnormally high: >=100 bpm.
PR interval: abnormally high: >=210 msec.
QRS interval: abnormally low: <=50 msec, abnormally high: >=120 msec.
QT interval: abnormally low: <=200 msec, abnormally high: >=500 msec.

QTc Interval Results Show a Greater Incidence of High Outliers in Some Pal group Compared to Placebo.

The table below shows results on outliers on QTc intervals (as provided in the SCS). These results show a numerically greater incidence in outliers on the maximum increase in QTc interval from the average pre-dose values to DB treatment values (for the <30 msec, and 30-60 msec categories) in the HD Pal group (15 mg) compared to the placebo and olanzapine groups. However, the numerical group differences between the HD Pal group and placebo or olanzapine groups were small.

The over 60 msec category also showed a slightly higher incidence in at least the 12 mg Pal group for increased QTc for all methods for calculating QTc. However, in most cases only 1 subject met the over 60 msec criterion level. The exception was with QTc Bazett's (QTcB) which is a method for QT interval correction that is intended for correcting for low heart rate values. Since heart rate generally increased with Pal treatment QTcB interval results may be misleading, at least regarding the magnitude of a potential QT prolongation effect.

Table 90: Distribution of Maximum Changes From Average Predose Value in Corrected QT Values (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
QTcLD	350	124	232	242	238	113	949	357
<30 (ms)	318 (91)	118 (95)	214 (92)	223 (92)	219 (92)	100 (88)	874 (92)	315 (88)
30-60 (ms)	32 (9)	6 (5)	18 (8)	19 (8)	18 (8)	13 (12)	74 (8)	41 (11)
>60 (ms)	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
QTcF	350	124	232	242	238	113	949	357
<30 (ms)	308 (88)	118 (95)	208 (90)	221 (91)	212 (89)	96 (85)	855 (90)	308 (86)
30-60 (ms)	42 (12)	6 (5)	24 (10)	21 (9)	25 (11)	16 (14)	92 (10)	48 (13)
>60 (ms)	0	0	0	0	1 (<1)	1 (1)	2 (<1)	1 (<1)
QTlc	350	124	232	242	238	113	949	357
<30 (ms)	317 (91)	117 (94)	213 (92)	225 (93)	218 (92)	99 (88)	872 (92)	318 (89)
30-60 (ms)	33 (9)	7 (6)	19 (8)	17 (7)	19 (8)	14 (12)	76 (8)	38 (11)
>60 (ms)	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
QTcB	350	124	232	242	238	113	949	357
<30 (ms)	276 (79)	96 (77)	156 (67)	170 (70)	150 (63)	76 (67)	648 (68)	253 (71)
30-60 (ms)	68 (19)	25 (20)	74 (32)	71 (29)	82 (34)	34 (30)	286 (30)	97 (27)
>60 (ms)	6 (2)	3 (2)	2 (1)	1 (<1)	6 (3)	3 (3)	15 (2)	7 (2)

Note: Percentages calculated with the number of subjects per parameter as denominator.

The results below show a numerically greater incidence of outliers on maximum changes in QTc values in the Pal compared to placebo groups but group differences are small except for QTcB interval results.

QTcB interval results showed a remarkable incidence of outliers in Pal groups compared to the placebo group that appeared to be dose-dependent (incidence of 17% and 23% in the 15 mg and 12 mg Pal groups, an incidence of 15% or less in lower dose Pal groups and an incidence of 11% in the placebo group for outliers of 450 msec or greater on QTcB). QTcB results are difficult to interpret from at least the perspective of a magnitude of an effect on QT prolongation since QTcB is most appropriately used for low heart rates, rather than for elevations in heart rate which was observed with Pal treatment at least at some time-points that appeared to attenuate or become absent over time, as previously explained.

The incidence of QTcF prolongation of 450 to less than 480 msec was 2.9% greatest in the 12 mg Pal group compared to 1.7% in the placebo group. See the table below for additional results.

Table 88: Maximum Increases of Corrected QT Intervals From Average Predose Value
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Treatment Group and Evaluation at Average Predose															
	Placebo (N=355)				ER OROS PAL 3 mg (N=127)				ER OROS PAL 6 mg (N=235)				ER OROS PAL 9 mg (N=246)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD																
Maximum value																
Normal	345	0	0	345	121	1	0	122	226	0	0	326	238	0	0	238
>=450 - <480	5	0	0	5	1	1	0	2	5	1	0	6	3	1	0	4
>=480	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	350	0	0	350	122	2	0	124	231	1	0	232	241	1	0	242
QTcF																
Maximum value																
Normal	344	0	0	344	121	1	0	122	225	0	0	225	236	0	0	236
>=450 - <480	6	0	0	6	1	1	0	2	6	1	0	7	5	1	0	6
>=480	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	350	0	0	350	122	2	0	124	231	1	0	232	241	1	0	242
QTlc																
Maximum value																
Normal	344	0	0	344	121	1	0	122	226	0	0	226	235	0	0	235
>=450 - <480	6	0	0	6	1	1	0	2	5	1	0	6	6	1	0	7
>=480	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	350	0	0	350	122	2	0	124	231	1	0	232	241	1	0	242
QTcB																
Maximum value																
Normal	304	6	0	310	105	0	0	105	193	0	0	193	208	0	0	208
>=450 - <480	33	2	0	35	15	3	0	18	31	3	0	34	25	6	0	31
>=480	4	1	0	5	1	0	0	1	2	3	0	5	3	0	0	3
Total	341	9	0	350	121	3	0	124	226	6	0	232	236	6	0	242

Note: Normal(Norm)(<450 ms); >=450 ms - <480 ms(>=450); >=480 ms(>=480)

(continued)

Table 88: Maximum Increases of Corrected QT Intervals From Average Predose Value (continued)
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Treatment Group and Evaluation at Average Predose															
	ER OROS PAL 12 mg (N=242)				ER OROS PAL 15 mg (N=113)				Total Paliperidone (N=963)				Olanzapine 10 mg (N=364)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD																
Maximum value																
Normal	234	0	0	234	111	0	0	111	930	1	0	931	353	0	0	353
>=450 - <480	4	0	0	4	2	0	0	2	15	3	0	18	3	0	0	3
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	238	0	0	238	113	0	0	113	945	4	0	949	357	0	0	357
QTcF																
Maximum value																
Normal	230	1	0	231	111	0	0	111	923	2	0	925	353	0	0	353
>=450 - <480	7	0	0	7	2	0	0	2	21	3	0	24	3	0	0	3
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	237	1	0	238	113	0	0	113	944	5	0	949	357	0	0	357
QTlc																
Maximum value																
Normal	234	0	0	234	111	0	0	111	927	1	0	928	353	0	0	353
>=450 - <480	4	0	0	4	2	0	0	2	18	3	0	21	3	0	0	3
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	238	0	0	238	113	0	0	113	945	4	0	949	357	0	0	357
QTcB																
Maximum value																
Normal	183	0	0	183	94	0	0	94	783	0	0	783	294	1	0	295
>=450 - <480	43	7	0	50	16	2	0	18	130	21	0	151	55	4	0	59
>=480	3	2	0	5	1	0	0	1	10	5	0	15	2	1	0	3
Total	229	9	0	238	111	2	0	113	923	26	0	949	351	6	0	357

Note: Normal(Norm)(<450 ms); >=450 ms - <480 ms(>=450); >=480 ms(>=480)

See Section 7.1.3.3.G for descriptions of subjects with QT prolongation that may be considered remarkable cases or were reported as ADOs. A description of individual subjects could not be found in in-text sections of the SCS but were found in QT related sections in CSRs, by the undersigned reviewer.

Results of the Elderly Short-Term Phase III Trial (-302).

Results are shown below. The incidence of outliers on high heart rate was remarkably greater in the Pal group compared to the placebo group, while results on other parameters were clinically unremarkable.

Table 86: Number of Subjects with Treatment-Emergent Abnormal ECG Values During the Double-Blind Period (Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)
Heart rate	37	76
Abnormally high	2 (5)	19 (25)
Abnormally low	5 (14)	6 (8)
PR interval	36	76
Abnormally high	2 (6)	4 (5)
Abnormally low	0	0
QRS interval	37	76
Abnormally high	0	1 (1)
Abnormally low	0	0
QT interval	37	76
Abnormally high	0	0
Abnormally low	0	0

Note: Percentages calculated with the number of subjects per parameter as denominator.
Note: Heart rate: abnormally low: <=50 bpm, abnormally high: >=100 bpm.
PR interval: abnormally high: >=210 msec.
QRS interval: abnormally low: <=50 msec, abnormally high: >=120 msec.
QT interval: abnormally low: <=200 msec, abnormally high: >=500 msec.
Cross-reference: Mod5.3.5.1\R076477-SCH-302\Sec6.5.3

The results below (as provided in the SCS) show a greater incidence of outliers for prolonged QTcB interval in both categories (the 450 to less than 480 msec category and the 480 msec or longer category). As previously noted, the results on QTcB are difficult to interpret regarding the magnitude of a Pal treatment effect on QT prolongation since QTB is more appropriate when heart rate is low rather than elevated.

Table 89: Maximum Increases of Corrected QT Intervals From Average Predose Value (Study R076477-SCH-302)

	Treatment Group and Evaluation at Average Predose							
	Placebo (N=38)				ER OROS PAL (N=76)			
	Norm	≥450	≥480	Total	Norm	≥450	≥480	Total
QTcLD								
Maximum value								
Normal	30	0	0	30	63	1	0	64
≥450 - <480	4	3	0	7	5	4	0	9
≥480	0	0	0	0	2	1	0	3
Total	34	3	0	37	70	6	0	76
QTcF								
Maximum value								
Normal	30	0	0	30	62	1	0	63
≥450 - <480	4	3	0	7	6	4	0	10
≥480	0	0	0	0	2	1	0	3
Total	34	3	0	37	70	6	0	76
QTlc								
Maximum value								
Normal	30	0	0	30	64	1	0	65
≥450 - <480	4	3	0	7	4	4	0	8
≥480	0	0	0	0	2	1	0	3
Total	34	3	0	37	70	6	0	76
QTcB								
Maximum value								
Normal	27	0	0	27	39	1	0	40
≥450 - <480	4	4	1	9	19	10	0	29
≥480	0	1	0	1	2	4	1	7
Total	31	5	1	37	60	15	1	76

Note: Normal(Norm)(<450 ms); >=450 ms - <480 ms(>=450); >=480 ms(>=480)

QTcB interval results showed a remarkable incidence of outliers in Pal and placebo groups as shown in the table below (copied from the SCS) with a greater incidence in the Pal group. Overall the Pal group showed slightly greater incidence of outliers in the 30 msec and over categories compared to the placebo group for QTc interval using any given method for calculation QTc, except for QTcB which showed larger group differences, as shown below. The magnitude of QTcB changes are difficult to interpret since QTcB is more appropriate in the presence of low rather than elevated heart rate, as previously discussed.

These observations that appear to show a drug effect on QTc prolongation were revealed despite serious limitations of this elderly Phase III trial which had small sample sizes, particularly in the placebo group and used a flexible dose design (3-12 mg/day) rather than examining a fixed

dose-response curve, along with other limitations that can impact on the ability to capture a real drug effect on QT interval (e.g. assessments were not timed specifically to capture a given subject near Tmax of Pal exposure).

Table 91: Distribution of Maximum Changes From Average Predose Value in Corrected QT Values (Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)
QTcLD	37	76
<30 (ms)	33 (89)	65 (86)
30-60 (ms)	4 (11)	10 (13)
>60 (ms)	0	1 (1)
QTcF	37	76
<30 (ms)	33 (89)	64 (84)
30-60 (ms)	4 (11)	11 (14)
>60 (ms)	0	1 (1)
QTlc	37	76
<30 (ms)	33 (89)	66 (87)
30-60 (ms)	4 (11)	9 (12)
>60 (ms)	0	1 (1)
QTcB	37	76
<30 (ms)	30 (81)	54 (71)
30-60 (ms)	7 (19)	21 (28)
>60 (ms)	0	1 (1)

Note: Percentages calculated with the number of subjects per parameter as denominator.
Note: All of the increases of >60 msec in corrected QT intervals were observed in 1 subject, Subject 200723.
Cross-reference: Mod5.3.5.1\R076477-SCH-302\Sec6.5.3.2

See Section 7.1.3.3. G for a description of ADOs of QT prolongation in the elderly Phase III trial.

Results of Ongoing Open-Label Extension Trials (-702 through -705).

Reviewer Comment. *The results below (as provided in the SCS) show a higher incidence of outliers for each of the following:*

- *High heart rate than for low heart rate and for*
- *High PR interval than for low PR interval.*

In the absence of a control group the results are difficult to interpret but they are consistent with previously described results of placebo controlled short term trials that showed evidence for a drug-induced increase in heart rate and small potential effects on PR prolongation, but the later observation was inconsistent across Pal groups. .

Table 87: Number of Subjects With Treatment-Emergent Abnormal ECG Values During the Open-Label Period
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
Heart rate	106	128	173	504	103	143	382	775
Abnormally high	32 (30)	34 (27)	21 (12)	90 (18)	28 (27)	40 (28)	81 (21)	164 (21)
Abnormally low	3 (3)	9 (7)	2 (1)	30 (6)	2 (2)	5 (3)	7 (2)	44 (6)
PR interval	105	128	172	504	103	143	380	775
Abnormally high	1 (1)	3 (2)	2 (1)	10 (2)	0	3 (2)	3 (1)	16 (2)
Abnormally low	0	0	0	0	0	0	0	0
QRS interval	106	128	173	504	103	143	382	775
Abnormally high	1 (1)	2 (2)	1 (1)	2 (<1)	1 (1)	0	3 (1)	4 (1)
Abnormally low	0	0	0	0	0	0	0	0
QT interval	106	128	173	504	103	143	382	775
Abnormally high	0	0	0	0	0	0	0	0
Abnormally low	0	0	0	0	0	0	0	0

Note: Percentages calculated with the number of subjects per parameter as denominator.
Note: Heart rate: abnormally low: <=50 bpm, abnormally high: >=100 bpm.
PR interval: abnormally high: >=210 msec.
QRS interval: abnormally low: <=50 msec, abnormally high: >=120 msec.
QT interval: abnormally low: <=200 msec, abnormally high: >=500 msec.

The tables below show up to 2.8% of Pal subjects (in the DB Pal/OL Pal > 3 month subgroup) who were outliers in QTc F,QTcLD, QTcL intervals of 450 msec or greater during OL treatment (OL treatment was 3-12 mg/day flexible dose in all subjects in these OL trials). Note that this large group of subjects (N=503 of which over 50 subjects are reported to have been in at least 24 weeks of the OL treatment phase) were in the over 3 month group including receiving DB Pal treatment in lead-in studies. The incidence for outliers in the < 3month subgroup of this DB Pal/OL Pal group was 2.3% or less for QTcF, QTcLD and QTcL interval prolongation. These results compare to an incidence of outliers of at least 450 msec on QTcF, QTcLD, QTcL intervals in the non-elderly short-term trial dataset, as follows (from studies -303, -304 and -305, combined and as previously shown):

- *3% or less among Pal groups (3, 6, 9, 12, and 15 mg/day groups)*
- *1.7% or less in the placebo group*

As with the short term trial dataset the QTcB interval showed the most remarkable Pal group incidence of outliers (of 450 msec or greater) as follows:

- *An incidence of approximately 12% in the over 3 month Pal-DB/Pal-OL subgroup*

The above results are compared to the following incidence of outliers on QTcB interval of at least 450 msec in the non-elderly short term trial dataset, as follows:

- *17% in the 15 mg Pal group,*
- *23% in the 12 mg Pal group,*
- *15% or less in lower dose Pal groups (3, 6 and 9 mg groups) and*
- *11% in the placebo group.*

It is difficult to interpret results of OL, non-placebo controlled trials and compare results across different studies. However, the incidence observed in OL treated subjects did not exceed the incidence observed in the DB trials. Yet, the DB trials were better designed for capturing subjects near Tmax and included more frequent ECG assessments.

Table 92: Maximum Increases of Corrected QT Intervals From Average Predose Value (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Treatment Group and Evaluation at Average Predose															
	Pla/Pali <=3 months (N=107)				Pla/Pali >3 months (N=128)				Pali/Pali <=3 months				Pali/Pali >3 months (N=505)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD																
Maximum value																
Normal	103	1	0	104	126	0	0	126	170	0	0	170	490	1	0	491
>=450 - <480	2	0	0	2	2	0	0	2	1	2	0	3	6	5	0	11
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	105	1	0	106	128	0	0	128	171	2	0	173	497	6	0	503
QTcF																
Maximum value																
Normal	102	1	0	103	126	0	0	126	169	0	0	169	488	1	0	489
>=450 - <480	3	0	0	3	2	0	0	2	2	2	0	4	8	4	0	12
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2
Total	105	1	0	106	128	0	0	128	171	2	0	173	497	6	0	503
QTlc																
Maximum value																
Normal	103	1	0	104	126	0	0	126	169	0	0	169	490	1	0	491
>=450 - <480	2	0	0	2	2	0	0	2	2	2	0	4	6	5	0	11
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	105	1	0	106	128	0	0	128	171	2	0	173	497	6	0	503
QTcB																
Maximum value																
Normal	86	0	0	86	110	3	0	113	150	2	0	152	438	6	0	444
>=450 - <480	15	3	0	18	14	1	0	15	15	5	0	20	44	13	0	57
>=480	1	1	0	2	0	0	0	0	0	1	0	1	0	2	0	2
Total	102	4	0	106	124	4	0	128	165	8	0	173	482	21	0	503

Note: Normal(Norm)(<450 ms); >=450 ms - <480 ms(>=450); >=480 ms(>=480)

(continued)

Appears This Way On Original

Table 92: Maximum Increases of Corrected QT Intervals From Average Predose Value (continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Treatment Group and Evaluation at Average Predose															
	- Olan/Pali <=3 months (N=106) -				- Olan/Pali >3 months (N=143) -				- Total Pali <=3 months (N=391) -				- Total Pali >3 months (N=776) -			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD																
Maximum value																
Normal	103	0	0	103	143	0	0	143	376	1	0	377	759	1	0	760
>=450 - <480	0	0	0	0	0	0	0	0	3	2	0	5	8	5	0	13
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	103	0	0	103	143	0	0	143	379	3	0	382	768	6	0	774
QTcF																
Maximum value																
Normal	103	0	0	103	142	0	0	142	374	1	0	375	756	1	0	757
>=450 - <480	0	0	0	0	1	0	0	1	5	2	0	7	11	4	0	15
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2
Total	103	0	0	103	143	0	0	143	379	3	0	382	768	6	0	774
QTlc																
Maximum value																
Normal	103	0	0	103	142	0	0	142	375	1	0	376	758	1	0	759
>=450 - <480	0	0	0	0	1	0	0	1	4	2	0	6	9	5	0	14
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	103	0	0	103	143	0	0	143	379	3	0	382	768	6	0	774
QTcB																
Maximum value																
Normal	94	0	0	94	126	1	0	127	330	2	0	332	674	10	0	684
>=450 - <480	8	1	0	9	14	2	0	16	38	9	0	47	72	16	0	88
>=480	0	0	0	0	0	0	0	0	1	2	0	3	0	2	0	2
Total	102	1	0	103	140	3	0	143	369	13	0	382	746	28	0	774

Note: Normal(Norm)(<450 ms); >=450 ms - <480 ms(>=450); >=480 ms(>=480)

It is critical to note the higher incidence of outliers in the over 3 month subgroups compared to the ≤ 3 month subgroups for subjects who continued on active drug in contrast to subjects that previously received DB placebo (in which the ≤ 3 month and > 3 month subgroups were generally similar on the incidence of outliers).

See results from 120-Day SUR showing a similar numerical trend for greater incidence with increasing exposure.

Table 93: Distribution of Maximum Changes From Average Predose Value in Corrected QT Values (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) N (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
QTcLD	106	128	173	503	103	143	382	774
<30 (ms)	97 (92)	115 (90)	166 (96)	462 (92)	102 (99)	130 (91)	365 (96)	707 (91)
30-60 (ms)	9 (8)	13 (10)	7 (4)	40 (8)	1 (1)	13 (9)	17 (4)	66 (9)
>60 (ms)	0	0	0	1 (<1)	0	0	0	1 (<1)
QTcF	106	128	173	503	103	143	382	774
<30 (ms)	94 (89)	114 (89)	166 (96)	460 (91)	102 (99)	127 (89)	362 (95)	701 (91)
30-60 (ms)	12 (11)	14 (11)	7 (4)	42 (8)	1 (1)	16 (11)	20 (5)	72 (9)
>60 (ms)	0	0	0	1 (<1)	0	0	0	1 (<1)
QTlc	106	128	173	503	103	143	382	774
<30 (ms)	97 (92)	116 (91)	168 (97)	463 (92)	102 (99)	129 (90)	367 (96)	708 (91)
30-60 (ms)	9 (8)	12 (9)	5 (3)	39 (8)	1 (1)	14 (10)	15 (4)	65 (8)
>60 (ms)	0	0	0	1 (<1)	0	0	0	1 (<1)
QTcB	106	128	173	503	103	143	382	774
<30 (ms)	78 (74)	99 (77)	150 (87)	401 (80)	86 (83)	106 (74)	314 (82)	606 (78)
30-60 (ms)	26 (25)	26 (20)	22 (13)	97 (19)	16 (16)	36 (25)	64 (17)	159 (21)
>60 (ms)	2 (2)	3 (2)	1 (1)	5 (1)	1 (1)	1 (1)	4 (1)	9 (1)

Note: Percentages calculated with the number of subjects per parameter as denominator.

Results of Ongoing Trials -301 and -701
Results from these ongoing trials are not provided in the original submission since they are ongoing with blinded data.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Refer to Sections 7.1.1-3 regarding ADOs, SAEs and deaths in the study. Also refer to Sections 7.1.3.3 and 7.1.4.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

The sponsor did not conduct any clinical studies relevant to carcinogenicity and studies were not designed to explore potential carcinogenicity effects. According to the sponsor their postmarketing data fails to show a signal for tumors (as described on page 236 of SCS).

7.1.12 Special Safety Studies

The following lettered subheadings were selected (rather than numbered subheadings) to simplify the layout of this subsection for the reader (rather than increasing the number of digits from 7.1.12 to 7.1.12.1, etc).

A. A Special Safety Study on QT Prolongation Effects of Paliperidone, Study R076477-SCH-1009 (-SCH-1009).

Summary of the Objective and Study Design of Study –SCH-1009.
The following describes the protocol which was reviewed as a special protocol assessment (6/25/04 N050 MS submission) and as an amended protocol (N089 12/14/04 submission) under IND 65850.

This DB, active-moxifloxacin controlled, multicenter (17 US sites) study examined the effects of IR Paliperidone to placebo treatment (in a cross-over design) on QT interval in patients with schizophrenia or schizoaffective disorder (18-50 years old, generally healthy with ECG parameter values within a normal cut- off value). The study was conducted in an inpatient setting.

Treatment. All subjects will first receive placebo on Day 1 and subjects commenced active treatment on Day 2 as follows (placebo dummy dosing was employed and all treatment capsules were identical in appearance):

- IR Pal group: 4 mg po on Day 2, 6 mg on Day 3, and 8 mg QD on Days 4-8.
- Moxifloxacin group: placebo treatment with dummy dosing on Days 1-7, then a single dose (SD) of 400 mg po moxifloxacin on Day 8

All treatment capsules were identical in appearance and placebo dummy dosing was employed to maintain the DB study design.

Key Eligibility Criteria
The following are selected, key inclusion criteria (copied from the CSR) that included meeting specified values on ECG parameters and on body weight:

- Men or women between the ages of 18 and 50 years, inclusive;
- Diagnosis of schizophrenia or schizoaffective disorder as defined by DSM-IV criteria, with no exacerbation of psychosis for at least 3 months before screening;
- Normal 12-lead ECG, with:
  - Normal sinus rhythm (heart rate between 50 and 100 beats per minute [bpm]);
  - QTcB interval ≤430 ms for men, and ≤450 ms for women;
  - QRS interval <110 ms;
  - PR interval <200 ms;
- Weight ≥50 kg (≥110 lb), with a body mass index (BMI) ≥18 and ≤35 kg/m^2;

The following are selected, key exclusion criteria that included meeting outlier criteria relevant to cardiac related parameters or having pre-existing conditions or risk factors (copied from the CSR) :

- Clinically significant abnormality on ECG at screening or on Day -1 of the study;
- Heart rhythm disturbance known or suggested by history, or demonstrated on ECG at screening;
- Blood pressure outside the normal range (supine systolic blood pressure <90 or >140 mmHg and/or diastolic blood pressure <50 or >90 mmHg);
- Unusual T-wave morphology in a majority of the ECG leads (e.g. bifid T waves, low T waves) or prominent U waves at screening;
- History of additional risk factors for TdP, such as heart failure, hypokalemia, family history of known long QT syndrome (LQTS), or sudden unexplained death at a young age (≤ 40 years) in a first degree relative such as a biological parent, sibling, or offspring;
- More than 10 cigarettes smoked per day;

Limited use of ibuprofen, benztropine, lorazepam and zolpidem treatment were permitted, as needed for appropriate symptoms (as specifed in the CSR) within restrictions outlined in Section 3.8 of the CSR (also benztropine or lorazepam could not be given during 6 hours prio to ECG recordings).

ECG and PK Assessments ECG assessments and blood samples for Paliperidone plasma levels were conducted at multiple time-points from Day 1 of placebo treatment, Day 2, Day 3-8 during active treatment, as well as on post-treatment ECG assessments on Days 9 and 10 after the 8-day blinded treatment phase. Assessments were also included on time-points near the anticipated Tmax after each daily dose on Days 1-4 and Day 8 (including a pre-dose assessment on these days) and at similar time-points on the 2 post-treatment days, Days 9 and 10 (corresponding to the same time-points used on treatment Days 1-4 and 8). Pre-dose assessments will be conducted on all treatment days (a -24 hour assessment on Day -1 will be conducted) and at the same corresponding time on each post-treatment day. Sections 9.3 and 9.3.1 of the protocol (under the IND) described ECG assessment methods and ECG reading methods. These sections also describe methods addressing potential confounding variables such as activity prior to readings, diurnal effects, effects of meals and others.

Tables 10.4 and 10.5 in the Appendix of this review provide the study schedule and the schedule for ECG assessments and PK blood sampling, respectively (as provided in the CSR).

Other Safety Assessments. Vital signs (no orthostatic measures) will be conducted at baseline and at the end of the study (not during treatment). Laboratory assessments and recording adverse events are included as safety assessments and screening tests will be performed as specified and as listed in the Time and Events Schedule in Table 10.3 series in the appendix of this review.

Concomitant Medications. Benztropine, lorazepam, zolpidem, ibuprofen or acetaminophen are allowed concomitant drugs on a PRN basis (as specified in Section 8). However, benztropine and lorazepam are not permitted on the days of ECG assessments. The following information was provided on concomitant medication use during the study. The table below was a part of the sponsor table in which the incidence of the more commonly used medications are shown (an incidence of at least 5%).

Attachment 1.4.2: Concomitant Therapies Administered Between Days 1 and 8 (Ph Analysis Set)

STUDY R076477-SCH-1009

Output DSUB.07: Summary of Concomitant Therapies within 8 Days of Start of Study Medic

Analysis Set: PD
Prior/concomitant Medication: Concom

Medication Generic Term	PALIPERIDONE (N=42) n (%)	MOXIFLOXACIN (N=57) n (%)	Total (N=99) n (%)
Lorazepam	26 (62)	31 (54)	57 (58)
Zolpidem tartrate	20 (48)	19 (33)	39 (39)
Ibuprofen	9 (21)	10 (18)	19 (19)
Paracetamol	3 (7)	9 (16)	12 (12)
Benzatropine mesilate	6 (14)	1 (2)	7 (7)
Zolpidem	1 (2)	6 (11)	7 (7)
Famotidine	1 (2)	4 (7)	5 (5)
Multivitamins	1 (2)	3 (5)	4 (4)
Sertraline hydrochloride	2 (5)	2 (4)	4 (4)
Amlodipine besilate	1 (2)	2 (4)	3 (3)
Hydrocortisone	0	3 (5)	3 (3)
Mylanta	2 (5)	1 (2)	3 (3)
Cepacol lozenge	0	2 (4)	2 (2)
Docusate sodium	1 (2)	1 (2)	2 (2)
Fluoxetine hydrochloride	1 (2)	1 (2)	2 (2)
Lansoprazole	0	2 (4)	2 (2)
Lisinopril	2 (5)	0	2 (2)

Concomitant Cardiovascular Conditions
Upon request the sponsor provided information on pre-existing cardiovascular conditions.

Reviewer Comment. *The most common cardiovascular condition was hypertension with a few subjects showing heart rate abnormalities (e.g. intermittent bradycardia or rapid pulse, each in 1 subject) or ECG abnormalities (e.g. first degree AV block in 1 subject, T wave abnormality in another subject).*

STUDY R076477-SCH-1009

Output: Medical History: Cardiovascular Abnormalities Reported at Screening

Analysis Set: Safety

Treatment Arm	Subject Number	Sex	Age	Reported Term for Condition
MOXIFLOXACIN	109021	MALE	46	SINUS BRADYCARDIA - INTERMITTENT
	109071	MALE	51	HYPERTENSION
	109086	MALE	46	PALPITATIONS BEGINNING IN 2000, ENDING IN 2001 DUE TO INCREASE IN DOSAGE OF SEROQUEL. HIGH AND LOW HEART BEAT.
	109098	MALE	23	HYPERTENSION MAR 2001 - MAY 2001
	109112	MALE	47	LATE ENTRY: HAS BEEN TREATED WITH NORVASC & HYPERTENSION HAS REMAINED STABLE 1SMAROS
	109121	MALE	31	POOR HEART SURGERY DUE TO STAB WARD 1997
	109126	MALE	27	TERMINALLY NEGATIVE IN V1
	109133	MALE	46	HYPERCHLORESTEROLEMIA
	109150	MALE	27	T WAVE ABNORMALITIES
	109157	MALE	42	HISTORY OF LABIL HYPERTENSION
	109163	FEMALE	46	DILATED CARDIOMYOPATHY - 1997
	109197	MALE	40	H/O HYPERTENSION CONTROLLED WITH DIET; LEFT VENTRICULAR HYPERTROPHY
	109218	FEMALE	41	PREGNANCY INDUCED HIGH BLOOD PRESSURE IN 1991. CONTROLLED WITH MEDICATION.
	109220	MALE	28	HYPERTENSION
	109237	FEMALE	48	CONTINUOUS HEART MURMUR SINCE 1970 CONT HIGH BLOOD PRESSURE SINCE 2000, TREATED WITH BENICAR
PALIPERIDONE	109024	MALE	47	HYPERTENSION; STABLE ON MEDICATION
	109029	FEMALE	32	HX OF CHEST DISCOMFORT, CHEST TENDERNESS
	109047	MALE	46	HTN - START 2000, STOP 2003
	109064	FEMALE	48	RAPID PULSE - RESOLVED
	109072	MALE	43	HYPERTENSION
	109099	MALE	42	PROLONGED PR INTERVAL FIRST DEGREE A-V BLOCK
	109103	MALE	39	HYPERTENSION ONSET 2002
	109135	MALE	37	HYPERTENSION WITH HIGH CHOLESTASIS
	109159	FEMALE	31	HEART MURMUR AS A CHILD
	109166	MALE	42	HIGH BLOOD PRESSURE
	109203	MALE	46	HISTORY OF HYPERTENSION SINCE 2002 STABLE AND CONTROLLED
	109223	MALE	50	HYPERTENSION

Pharmacogenomics Blood samples were collected (upon informed consent) for genetic analysis, since some genotypes may be associated with QT prolongation effects.

Calculations of QTc Interval and Dav-averaged QTcLD Parameters

The following outlines equations used for calculation QTc intervals:

- Linear Derived: QTcLD (sec) = QT+b[1–RR], where b is the estimated slope using a linear regression techniques as described in Section 3.11.2.1 of the CSR. Also refer to Section 7.1.9.3.1. This method of QTc is described by the sponsor as a linear model that "incorporates all drug free QT/RR interval data" and is also intended to correct for study specific differences in this data.
- Bazett: $QTcB=QT/RR_{0.5}$
- Sagie: QTlc=QT + 0.154 (1-RR), and
- Fridericia: $QTcF=QT/RR_{(1/3)}$

Calculation of Day Averaged ECG Parameters

The following describes methods for calculating day-averaged QTc parameters (copied from the CSR):

> The primary endpoint was the difference with placebo (Day 1) in day-averaged QTcLD values. Day-averaged parameters were calculated for the 7 days with complete ECG profiles: Days 1 to 4 and 8 to 10. Since times between ECG intervals on a day are unequally spaced, the day-average was calculated as a weighed mean: $\left(\sum_{i=1}^{10}\left(\frac{(V_i+V_{i-1})}{2}*(T_i-T_{i-1})\right)\right)\Big/(T_{10}-T_0)$ with V_i the value (e.g. QTcLD) at time T_i. T_0 being the first assessment on a day (scheduled at 8:00), T_1 being the next (scheduled at 8:30), continuing until the last T_{10} (scheduled at 20:00). Parameters were considered missing, if more than 3 values out of 11 constituting the average are missing. If more than 2 assessments between T_1 (+30min) and T_3 (+4h) were missing, the weighted average was set to missing.

Study Results

The summary tables and figures shown below were provided in the SCS or in the CSR of the submission.

Reviewer Comments on results shown below. *Note that maximal least square mean increases in QTcLD interval from baseline to a given post-dose time-point is at 1.5 hours post-dose on each Pal treatment day which is near the anticipated Tmax for this IR formulation. Note that greater prolongation occurs with higher dose-levels (when comparing results of the 8 mg dose-level to each of the 2 lower daily dose-levels of 4 mg and 6 mg, respectively) and over successive treatment days which includes successive treatment days in which the daily dose-level was fixed (between Days 4 and 8 during which Pal subject received a daily dose of 8 mg). However, the 6 mg dose-level (given on Day 3) shows a similar increase in QTc intervals to that observed with the lower daily dose-level of 3 mg given on Day 2. It is difficult to determine if the similar prolongation effects of Pal at these two lower dose-levels is reflecting a potential influence of time of exposure (e.g. where there may be some physiological adaptation to the QT prolongation effects with repeated or prolonged exposure) or if these findings truly reflect that the 3 mg and 6 mg dose-levels have a similar effect on QT interval. Finally, it is important to note that the QT prolongation effects are reversible upon dechallenge.*

Another critical consideration with interpreting the results is that a greater QT prolongation effect may have been observed at daily dose-levels above the 3 mg dose-level if Pal subject had not been titrated to the higher dose-levels. That is, a study using a fixed dose, parallel group design to examine different Pal dose-levels may have yielded greater prolongation effects at dose-levels above the 3 mg dose-level. Consider the possibility for a degree of physiological adaptation to a drug effect on QT prolongation that may occur over time with multiple dosing. The sponsor suggests that such an adaptation may be occurring based on results described later in this review Consequently, the daily dose-levels above 3 mg, (e.g. the 6 mg and 8 mg dose-levels employed in the study) may actually show greater QT prolongation effects in Pal-drug naïve subjects or in subjects that do not undergo adequate titration to the higher dose-levels.

While considering that QT prolongation effects at daily dose-levels above 3 mg may be greater than that observed in Study -1009, note that the least square mean values for QTcLD exceeded 10 msec at 1.5 hour post-dose on Day 8 in Pal subjects. The upper limit of the 90% confidence interval (CI) exceeded 10 msec at this same 1.5 hour post-dose time-point on Day 2 (the first day of Pal treatment which was at the 4 mg daily dose-level in which QTcLD was 11.9 msec), and again on Days 4 and 8 (12.3 and 13.6 msec, respectively). The upper limit of the 90% CI for QTcLD interval on Day 3 (at the 6 mg daily dose-level) reached 9.4 msec at the 1.5 hour post-dose time-point. None of the Pal subjects had prolonged QTc values (exceeding 450 msec for males or 470 msec for females) except for QTcB which was prolonged in 7 out of 72 Pal subjects (approximately 10%). However, 3-4% of subjects showed borderline prolongation of QTc interval during Pal treatment (values of 430-450 msec for men and 450-470 msec for women), except for QTcB which showed borderline prolongation in 31 out of 72 Pal subjects (43%).

26 to 28% of Pal subjects showed a 30-60 msec increase from baseline to their maximal on-treatment values in QTc interval for any of the correction methods, except for QTcB interval which showed a 30-60 msec increase in 82% of Pal subjects. None of the Pal subjects showed a QTc increase of greater than 60 msec, except for QTcB in which only 1 Pal subject showed an of over 60 msec increase. As previously described QTcB values are not considered accurate in determining the degree of QT prolongation since heart rate is increased by Pal.

Given the above comments, it is also notable the large between subject variance on plasma levels, the large effect of food on plasma levels based on food effect Phase I results, among other factors that can lead to higher plasma levels. PK results are shown below with further reviewer comments.

Table 108: Day-Averaged QTcLD: Least Square Mean Differences From Day 1 (Study R076477-SCH-1009: Per-Protocol Analysis Set)

Treatment Arm	Visit	Treatment Group	LSMean (SE)	LSMean Difference (SE)	90% CI on LSMean Difference[a,b]
IR Paliperidone (N=44)	Day 1	Placebo	387.6 (2.22)		
	Day 2	4 mg IR q.d.	390.6 (2.23)	3.0 (1.10)	(1.18; 4.79)
	Day 3	6 mg IR q.d.	388.1 (2.22)	0.6 (1.09)	(-1.23; 2.36)
	Day 4	8 mg IR q.d.	390.5 (2.23)	2.9 (1.10)	(1.13; 4.75)
	Day 8	8 mg IR q.d.	393.0 (2.22)	5.5 (1.09)	(3.66; 7.25)
	Day 9	Posttreatment	390.5 (2.22)	3.0 (1.09)	(1.18; 4.77)
	Day 10	Posttreatment	389.8 (2.22)	2.2 (1.09)	(0.45; 4.05)
Moxifloxacin (N=58)	Day 1	Placebo	391.8 (1.87)		
	Day 2	Placebo	391.8 (1.87)	-0.0 (0.84)	(-1.40; 1.36)
	Day 3	Placebo	390.6 (1.87)	-1.2 (0.84)	(-2.59; 0.17)
	Day 4	Placebo	391.1 (1.87)	-0.7 (0.84)	(-2.09; 0.67)
	Day 8	400 mg q.d.	396.1 (1.87)	4.3 (0.84)	(2.88; 5.64)
	Day 9	Posttreatment	393.1 (1.87)	1.3 (0.84)	(-0.10; 2.65)
	Day 10	Posttreatment	390.8 (1.87)	-1.0 (0.84)	(-2.38; 0.38)

[a] The 2-sided 90% confidence intervals around the mean difference in day-averaged QTcLD during and after paliperidone treatment compared with day-averaged QTcLD on during placebo treatment (Day 1) was constructed using the estimated least-squares means and variances from the mixed models with treatment as a fixed effect and subject as a random effect.

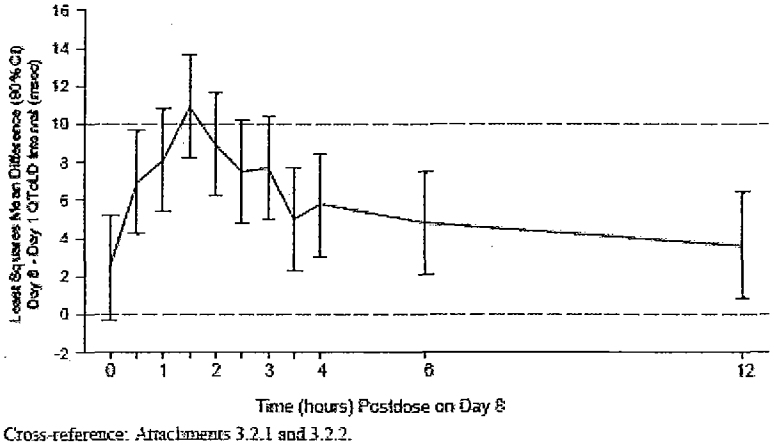
[b] The mean effect of IR paliperidone 8 mg at steady-state (Day 8) on QTc interval was considered "negative" if the 2-sided 90% confidence interval excluded 10 msec. Assay sensitivity was confirmed, i.e., moxifloxacin 400 mg had a positive effect on QTc interval if the 2-sided 90% confidence interval excluded 0 msec.

Cross-reference: Mod5.3.5.4\R076477- SCH-1009\Sec7.2.1.1.

Table 109: QTcLD: Least Square Mean Differences From Day 1 on Days 2, 3, 4, 8, 9, and 10 at Each Time Point (Study R076477-SCH-1009: Paliperidone-Treated Subjects [N=44] in the Per Protocol Analysis Set)

Time Postdose	LS Mean Difference	SE	90% CI LL	90% CI UL	LS Mean Difference	SE	90% CI LL	90% CI UL	LS Mean Difference	SE	90% CI LL	90% CI UL
	Day 2 (PAL 4 mg)				**Day 3 (PAL 6 mg)**				**Day 4 (PAL 8 mg)**			
Predose	0.70	1.66	-2.00	3.45	0.40	1.66	-2.36	3.11	1.00	1.66	-1.77	3.68
0.5 h	4.70	1.66	2.02	7.46	2.80	1.65	0.07	5.49	5.50	1.65	2.75	8.17
1.0 h	4.90	1.64	2.22	7.60	4.30	1.64	1.58	6.96	5.60	1.64	2.90	8.28
1.5 h	9.30	1.65	6.56	11.98	6.70	1.64	4.04	9.42	9.60	1.64	6.92	12.31
2.0 h	5.50	1.65	2.76	8.18	4.60	1.64	1.94	7.33	7.30	1.64	4.56	9.94
2.5 h	3.40	1.64	0.67	6.06	4.00	1.64	1.35	6.74	4.70	1.65	1.98	7.40
3.0 h	4.00	1.64	1.33	6.71	2.80	1.64	0.10	5.49	7.20	1.66	4.52	9.97
3.5 h	3.40	1.64	0.74	6.12	-0.10	1.64	-2.83	2.56	3.70	1.65	0.95	6.37
4.0 h	2.90	1.64	0.22	5.60	2.00	1.64	-0.65	4.74	3.20	1.65	0.52	5.93
6.0 h	2.00	1.64	-0.74	4.65	-1.30	1.64	-3.94	1.44	1.30	1.64	-1.37	4.01
12.0 h	1.80	1.65	-0.86	4.55	-1.10	1.66	-3.82	1.63	1.30	1.65	-1.45	3.96
	Day 8 (PAL 8 mg)				**Day 9 (Posttreatment)**				**Day 10 (Posttreatment)**			
Predose	2.50	1.66	-0.27	5.18	2.00	1.66	-0.74	4.74	0.90	1.66	-1.87	3.61
0.5 h	6.90	1.65	4.21	9.62	4.90	1.65	2.18	7.60	7.20	1.65	4.48	9.89
1.0 h	8.10	1.64	5.40	10.78	4.10	1.64	1.44	6.83	2.20	1.64	-0.51	4.87
1.5 h	10.90	1.64	8.24	13.62	5.00	1.64	2.26	7.65	2.70	1.64	0.04	5.42
2.0 h	8.90	1.64	6.22	11.60	5.30	1.65	2.63	8.04	1.70	1.64	-1.03	4.35
2.5 h	7.50	1.65	4.83	10.24	1.70	1.65	-1.02	4.39	0.40	1.64	-2.26	3.12
3.0 h	7.70	1.64	4.99	10.37	3.40	1.64	0.69	6.08	1.70	1.64	-1.03	4.35
3.5 h	5.00	1.64	2.29	7.67	4.00	1.64	1.31	6.69	1.50	1.64	-1.21	4.17
4.0 h	5.80	1.64	3.06	8.44	1.20	1.65	-1.53	3.89	1.90	1.64	-0.83	4.56
6.0 h	4.80	1.64	2.08	7.46	1.30	1.65	-1.40	4.01	0.90	1.64	-1.78	3.60
12.0 h	3.60	1.65	0.93	6.35	3.80	1.66	1.10	6.54	3.90	1.66	1.20	6.64

The following figure was found in the CSR. The least square mean difference of QTcLD from Day 1 (placebo treatment day) to each assessment time-point on Day 8 (the seventh day of Pal treatment) is shown (using a mixed model with fixed effects for study days, assessment time-points, that was fit to individual QTcLD values for each treatment group).



Cross-reference: Attachments 3.2.1 and 3.2.2.

The following tables summarize the incidence of QTc interval outliers (copied from the CSR).

Table 15: Number of Subjects With a Maximum Change in QTc Interval of 30 to 60 ms or ≥60 ms
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)			Placebo/Moxifloxacin (N=69)		
	Total	QTc Interval ↑ (ms)		Total	QTc Interval ↑ (ms)	
Parameter	n (%)	30-60	>60	n (%)	30-60	>60
QTcLD	19 (26)	19	0	12 (17)	12	0
QTcF	19 (26)	19	0	11 (16)	11	1
QTlc	20 (28)	20	0	13 (19)	13	0
QTcB	59 (82)	59	1	26 (38)	26	0

Number of subjects with a maximum increase in QTc of 30-60 ms or >60 ms at any time during the study relative to time-matched QTc intervals on Day 1 (placebo).

Cross-reference: Attachment 3.4.

Table 16: Number of Subjects With a Maximum QTc Interval That Was Borderline or Prolonged
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)			Placebo/Moxifloxacin (N=69)		
	Total	QTc Interval		Total	QTc Interval	
Parameter	n (%)	Borderline	Prolonged	n (%)	Borderline	Prolonged
QTcLD	2 (3)	2	0	5 (7)	5	0
QTcF	3 (4)	3	0	6 (9)	6	0
QTlc	2 (3)	2	0	5 (7)	5	0
QTcB	31 (43)	31	7	24 (35)	24	1

Note: QTcLD is a derived parameter.
Criteria for Borderline QTc: 430-450 ms for men, 450-470 ms for women
Criteria for Prolonged QTc: >450 ms for men, >470 ms for women

Cross-reference: Attachment 3.5

Table 17: Number of Subjects With Absolute QTc Prolongation ≥450 ms, ≥480 ms, or >500 ms
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)					Placebo/Moxifloxacin (N=69)				
		Maximum QTc Interval (ms)					Maximum QTc Interval (ms)			
	n	Normal	≥450	≥480	>500	n	Normal	≥450	≥480	>500
QTcLD	72	72	0	0	0	69	69	0	0	0
QTcF	72	72	0	0	0	69	69	0	0	0
QTlc	72	72	0	0	0	69	69	0	0	0
QTcB	72	63	8	1	0	69	63	6	0	0

Cross-reference: Attachment 3.6.

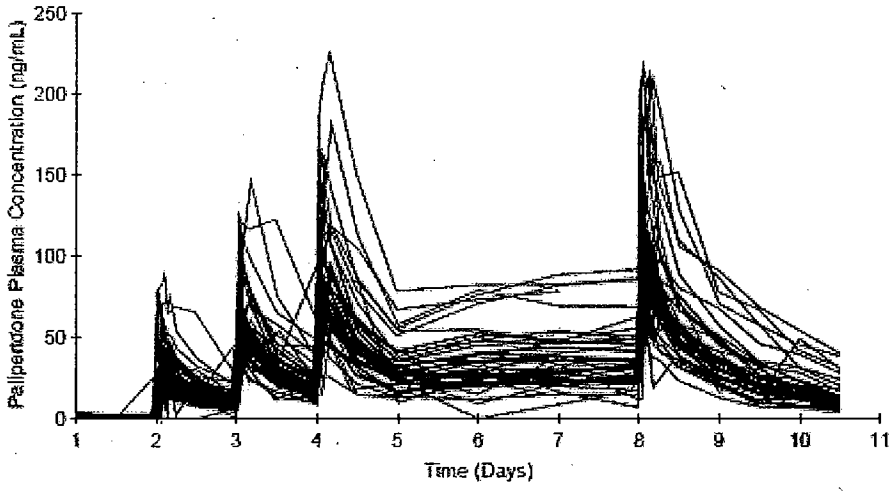
PK Results

The SCS indicates that steady state mean Cmax plasma levels of IR Pal during daily treatment with 8 mg IR Pal was 113 ng/L (using Day 8 data). According to the sponsor, this mean Cmax level is 2-fold higher than mean Cmax level with daily treatment of the highest dosage of Pal (ER OROS Pal formulation) used in the Phase III trials (mean Cmax=57.4 ng/mL with 15 mg OROS Pal/ daily).

Reviewer Comments. *Note that in the scatterplot below, of plasma levels of individual subjects over time, that more subjects exceeded 100 ng/ml on Day 8 (the fifth day on the 8 mg daily dose-level) compared to Day 4 (the first day of the 8 mg daily dose-level). Mean Cmax levels on these days could not be found in the in-text sections of the CSR but according to that described in the CSR steady state levels were reached by Day 6 (the third day at the 8 mg daily dose-level). However, according to that described in the CSR, steady state levels were reached by Day 6 (the third day at the 8 mg daily dose-level). Consequently one should not anticipate higher Cmax levels with longterm treatment beyond levels observed in Day 8. Yet, accumulation of the drug among other factors can also affect plasma levels, such as the known food effect on levels with Pal treatment. With respect to potential drug accumulation the T ½ is long (mean T ½ is 23.2 hours with a range of 10.6 to 51.1 hours, according to that described in the CSR. Furthermore, the relationship between dose-level and mean Cmax and mean AUC-24hr is not linear but instead a 3.2 and 3.5 times greater, respectively, at the 8 mg daily dose-level (on Day 8) compared to exposure at the 4 mg dose-level on day 2. This issue will be discussed later in this review, with respect to [redacted] OROS Pal and anticipated plasma levels relative to anticipated effects on QT prolongation based on results of Study -1009.*

The following table shows plasma levels of each individual subject over time, as provided in the CSR.

Figure 3: Overlay Plasma Concentration-Time Profiles of Paliperidone on Days 1 through 10
(Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



Cross-reference: Attachment 2.3.

The following table provides PK results (as provided in the CSR).

Table 11: Pharmacokinetic Parameters Calculated From the Paliperidone Concentration-Time Profiles on Days 2 through 8 (Study R076477-SCH-1009; Pharmacokinetic Analysis Set)

	Day 2				Day 3	Day 4	Day 5	Day 6	Day 7
	$C_{pre,D2}$ (ng/mL)	$C_{max,D2}$ (ng/mL)	$t_{max,D2}$ (h)	$AUC_{24,D2}$ (ng.h/mL)	$C_{pre,D3}$ (ng/mL)	$C_{pre,D4}$ (ng/mL)	$C_{pre,D5}$ (ng/mL)	$C_{pre,D6}$ (ng/mL)	$C_{pre,D7}$ (ng/mL)
N	63	63	63	58	58	52	49	49	49
Mean	BQL	35.2	2.07	437	10.4	20.7	30.2	35.0	36.9
SD	-	14.9	0.90	198	4.77	10.1	14.1	18.2	18.3
CV%	-	42.3	43.4	45.4	45.9	48.7	46.8	52.1	49.6
Median	BQL	32.7	2.05	420	9.86	18.7	27.1	29.9	33.1
Minimum	BQL	16.0	0.55	109	BQL	8.82	9.90	BQL	8.55
Maximum	26.2	89.3	4.08	1398	26.9	61.8	78.7	82.3	88.6

	Day 8								
	$C_{pre,D8}$ (ng/mL)	$C_{max,D8}$ (ng/mL)	$t_{max,D8}$ (h)	$C_{min,D8}$ (ng/mL)	AUC_{τ} (ng.h/mL)	$C_{avg,ss}$ (ng/mL)	FI (%)	λ_z (1/h)	$t_{\frac{1}{2},\lambda}$ (h)
N	46	42	42	43	42	42	42	40	40
Mean	37.1	113	2.15	34.6	1531	63.8	128	0.0321	23.2
SD	18.7	43.3	1.12	18.4	647	26.9	30.9	0.00908	6.6
CV%	50.4	38.4	52.1	53.3	42.2	42.2	24.3	28.3	28.4
Median	33.4	102	2.08	30.7	1353	56.4	124	0.0299	23.2
Minimum	6.95	59.8	0.52	6.95	649	27.1	84.2	0.0136	10.6
Maximum	92.0	218	6.08	90.9	3454	144	209	0.0653	51.1

Cross-reference: Attachment 2.6.

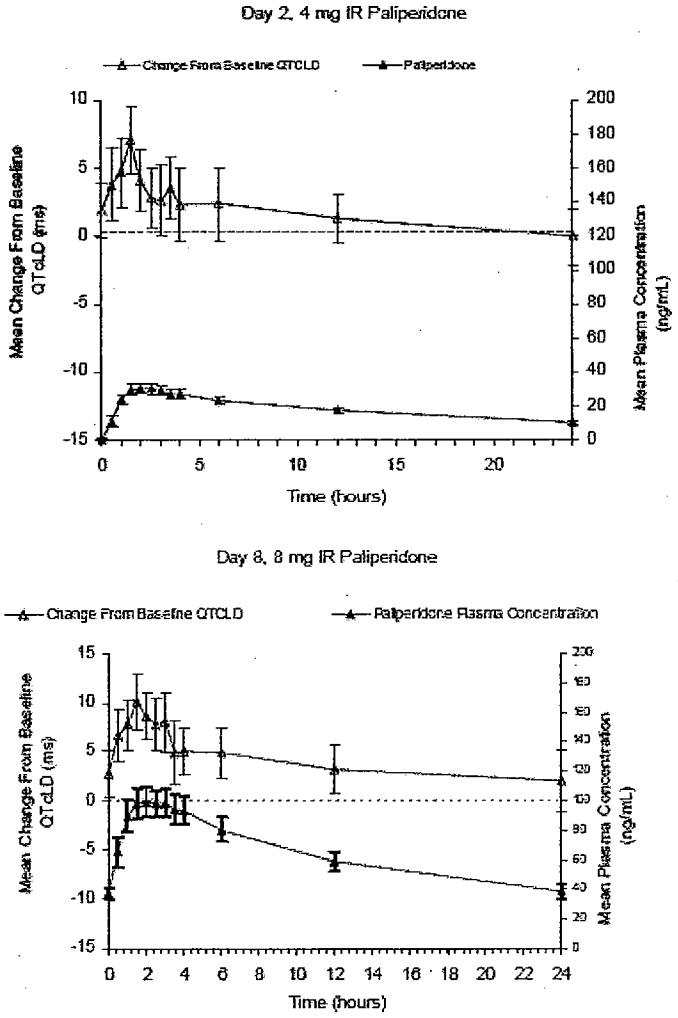
The Relationship between PK and QT Interval Effects of IR Pal

The sponsor indicates that an "apparent" positive relationship was observed between "peak plasma concentration" of IR Pal the mean increase from baseline on QTcLD interval (based on the results on the mean change in QTcLD from Day 1/placebo treatment, to Day 2/4 mg IR Pal treatment and Day 8/8 mg IR Pal and the time-matched mean plasma levels of Pal).

Yet, upon further examination of the PK-PD data (see figures below) the PK-PD relationship is more complex such that a given plasma level of Pal is not always associated with the same degree of QT prolongation effects. According to that described in the CSR, daytime variation in QTcLD influences the interpretation of the results in which the mean increase in QTcLD reaches a peak increase from pre-dose (or peak absolute values) at 4 hours post-dose on Day 1 (placebo treatment day) that was observed in the Pal group. According to the sponsor if mean values in QTcLD following Pal treatment are corrected for the day time variability in the placebo group, then Cmax more closely coincides with maximal mean QTcLD prolongation (see Figure 5 below).

The following figures illustrate mean changes in QTcLD in relation to mean plasma levels of Pal with mean values adjusted for "day-time variance" observed on the placebo treatment day, Day 1 (copied from the CSR).

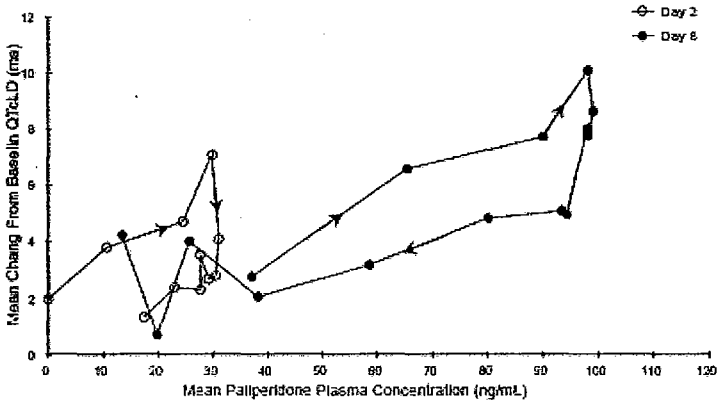
Figure 5: Mean (90% CI) Paliperidone Plasma Concentrations Versus Time-Matched Change From Baseline QTcLD Profiles as a Function of Time
(Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



The sponsor notes that while mean plasma levels remain elevated between 2 and 4 hours post-dose, that mean increases from baseline on QTcLD interval decline over time between the 2 and 4 hour time-points (as shown in the above figure with mean QTcLD values corrected for day time variability observed on the placebo treatment day, Day 1). According to that described in the CSR, these results suggest a potential physiological adaptation to QT prolongation effects with exposure of Pal over time. The figure below illustrates more clearly how initial increases in Pal plasma levels are associated with mean increases in QTcLD interval, yet these mean increases in QTcLD interval decrease in magnitude over subsequent time-points when Pal plasma levels remain constant near Cmax levels (see in the figure below that the mean QTcLD change from baseline decreases while peak mean Pal plasma levels remain elevated at close to

approximately 30 ng/ml on Day 2 or while peak levels remain elevated at close to approximately 95-100 ng/ml on day 8).

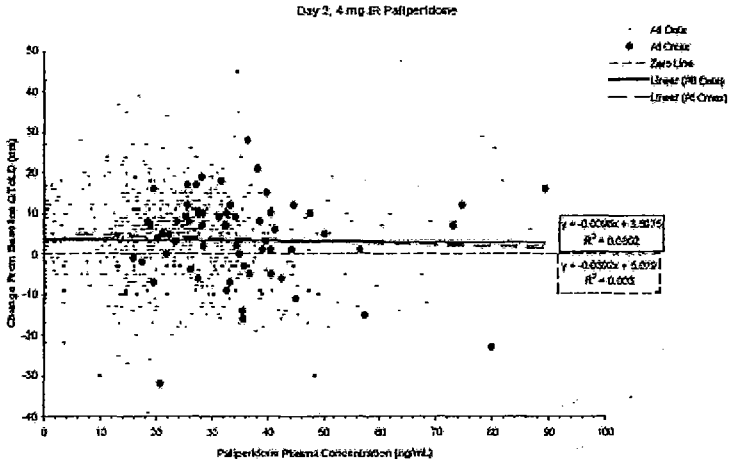
Figure 6: Mean Change From Baseline QTcLD
Versus Mean Paliperidone Plasma Concentration
(Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



Cross-reference: Attachment 4.5.

The figure below, copied from the CSR, further illustrates the complexity of the PK-PD relationship in which other confounding variables influencing PK and QT interval results must be considered in order to elucidate the role of PK on QT interval prolongation effects.

Figure 7: Scatter Plots of Change From Baseline QTcLD Versus
Plasma Concentration of Paliperidone
(Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



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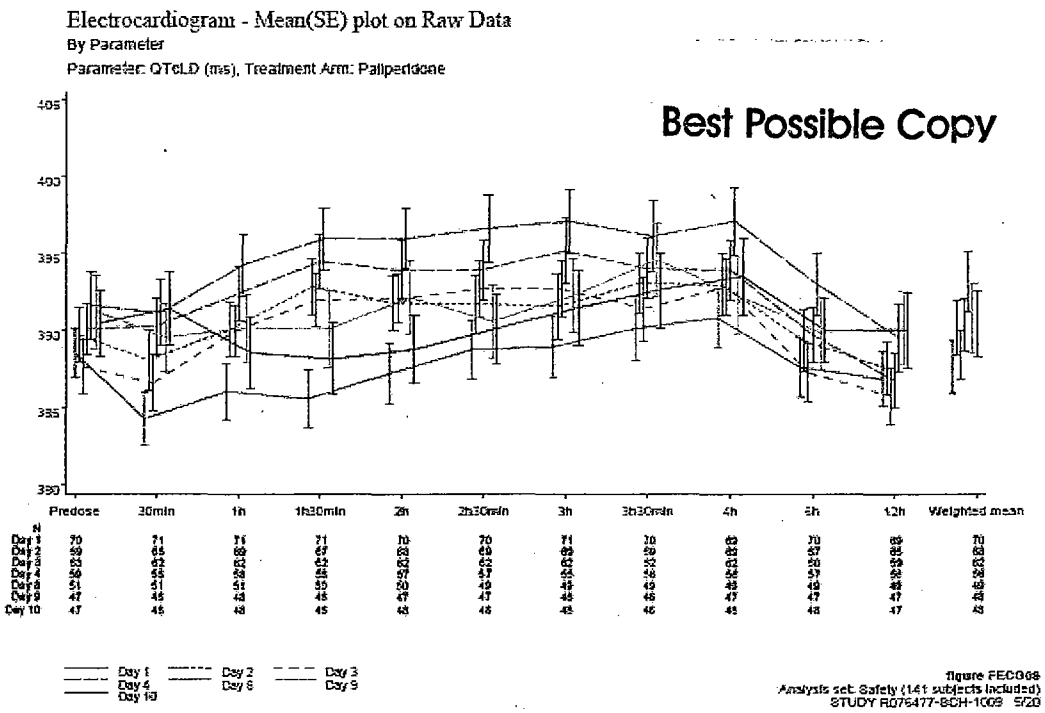
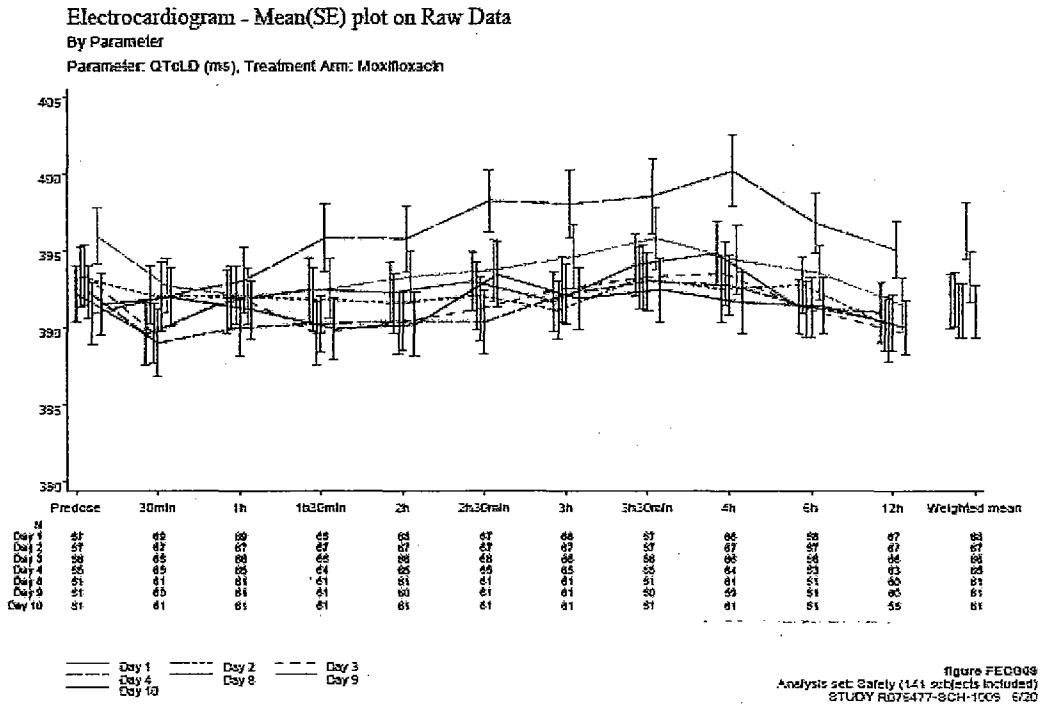
Cross-reference: Attachment 4.13.

Reveiwer Comments. *It is not clear to the undersigned reviewer how the sponsor corrected QTcLD interval data following Pal treatment to control for the day time variance in QTcLD QT inverval that was observed with placebo treatment of which the sponsor notes that peak increases were observed at 4 hours after placebo treatment. This approach may not be adequate, since it does not take into account potential variance across days and QT interval showed increases not only at the 4 hour post-dose time-point but also at other time-points. Statistical methods employed are also based on several assumptions. Figures below show raw mean QTcLD intervals over time on each treatment day of both groups (Pal group received placebo on Day 1, Pal on Days 2-8, then no treatment on Days 9 and 10, while the Moxifloxacin group received placebo on Days -7, then moxifloxacin on Day 8, followed by no treatment on Days 9 and 10). Note that the groups showed a similar magnitude of maximal QTcLD interval increases at Day 8 of treatment (when examining increases relative to pre-dose values or compared to placebo and post-treatment day values at time-points where differences were greatest for the given treatment group).*

Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



The figures below are for QTcF raw mean results over time by each treatment day

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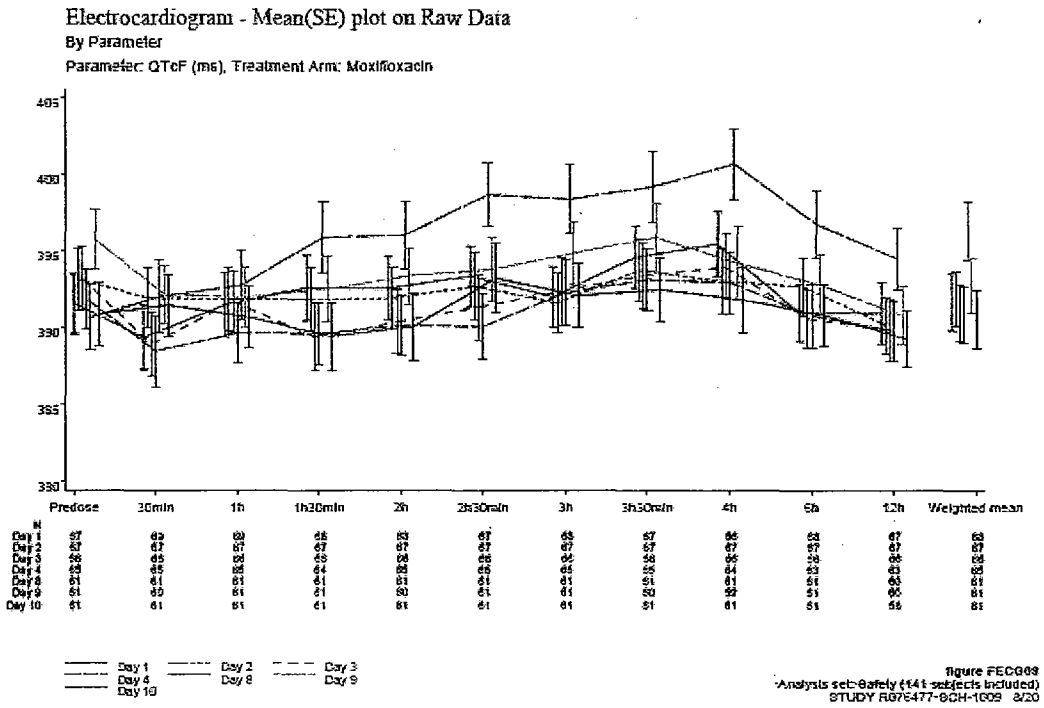

Note in the figures below that HR showed a remarkable increase following increases in QTcF and QTcLD.

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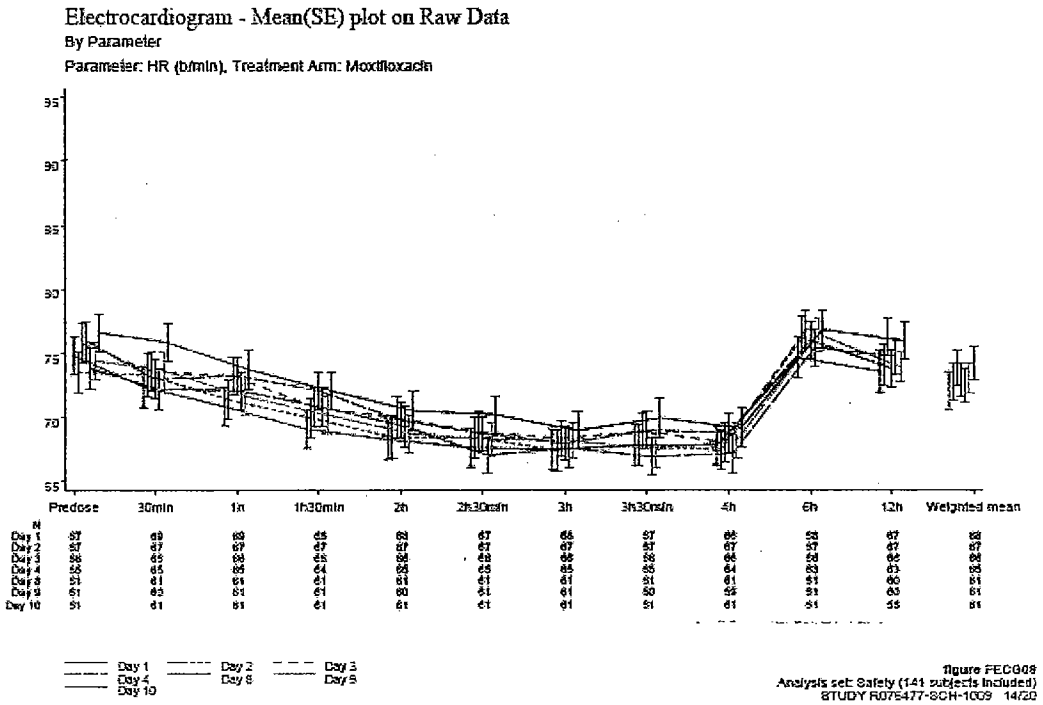
Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



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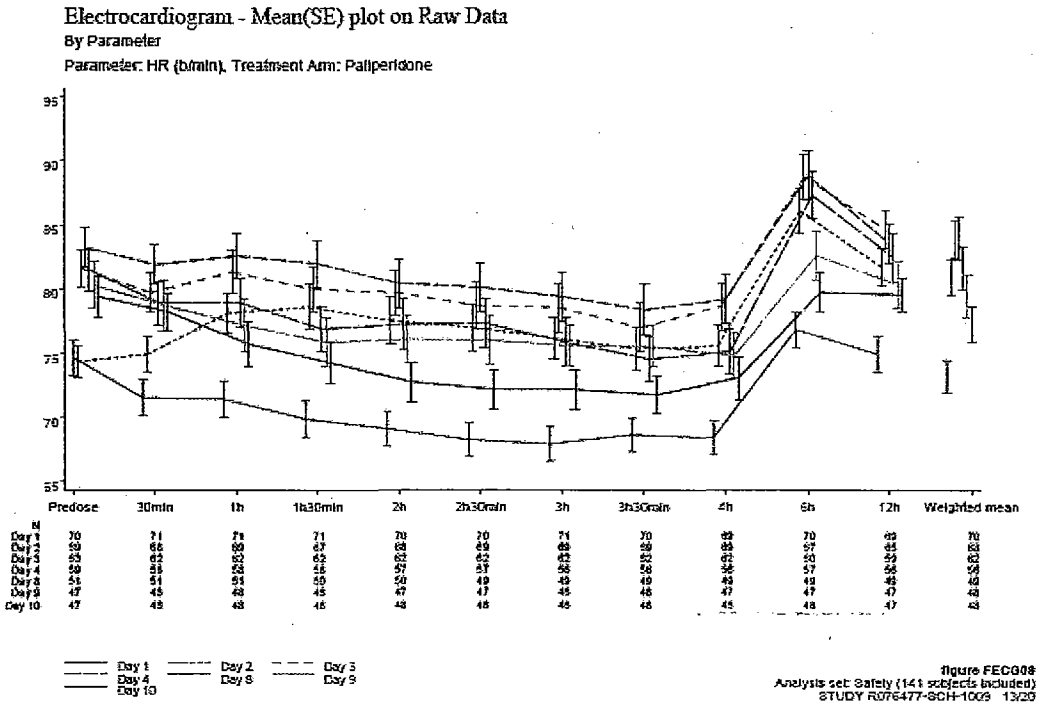
Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



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Analysis set: Safety (141 subjects included)
STUDY R076477-SCH-1009 13/29

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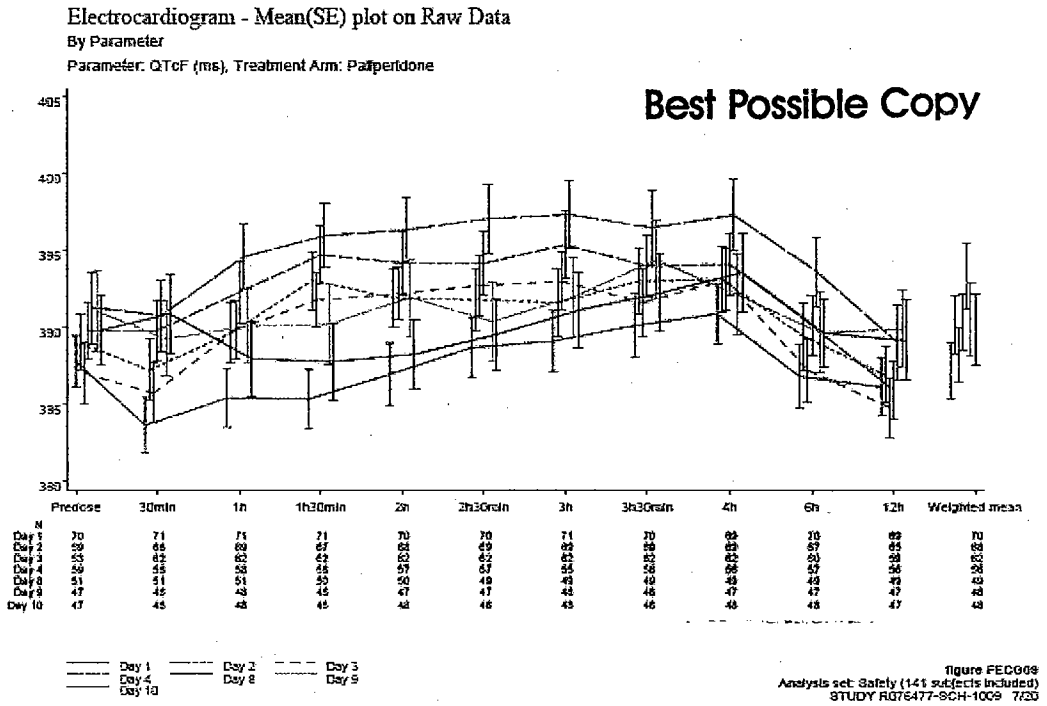
Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



See the figures below showing somewhat sustained elevations in mean QTcLD values between the time-point near Cmax for Pal plasma levels (which occurred at approximately 1.5-2 hours post-dose, as shown in the figures) to approximately 4 hours post-dose of each Pal treatment day, in which plasma levels continued to be elevated near Cmax levels. These results would suggest a close relationship between elevations in plasma elevations with increased QTcLD interval, at least during the first several hours (up to at least 4 hours) following daily dosing. It is not clear if such a relationship would continue to be observed with longterm treatment after steady state levels are achieved, since the study was not designed with this objective. Also one must consider other confounding variables that can lead to elevations in plasma levels or may increase Cmax levels over longterm treatment. Food effects are know to exist such that elevations can occur postprandial compared to the fasted state. The large between individual variance in plasma levels (based on Cmax and AUC values) also suggests the presence of other confounding variables that could lead to increased plasma levels that in turn may be associated with prolongation of QT interval. Consider the potential for accumulation of Pal with longterm treatment, particularly in organ tissues such as the myocardium.

The above factors that can result in higher Pal plasma levels and in turn, may result in greater QT prolongation effects become more critical when attempting to extrapolate results of Study - 1009 using an IR formulation to the ER, OROS formulation that the sponsor seeks to monitor. The CSR of this study indicates that the Day 8 Cmax levels of 8 mg daily IR Pal treatment in the study was 113± 43 (±SD) ng/ml, while Cmax of a 15 mg daily dose of ER OROS Pal used in

clinical trials was 57±30 ng/ml. Yet this comparison does not take into account an approximately 50% increase in plasma levels in the fed state compared to the fasted state, the potential for accumulation of the drug (also consider organ system concentrations and redistribution), potential gender differences and the large between individual variance on plasma levels. Furthermore, one must not only consider risk factors or variables adversely influencing PK, but also risk factors, pre-existing conditions and other variables that can adverse influence QT interval and Pal induced QT interval prolongation. For example, consider greater values observed in women versus men, the influence of pre-existing cardiac conditions, concomitant medications and other factors. A discussion on these issues and data relevant to these issues could not be found in the CSR of Study 1009 (e.g. gender specific results on PK or QT interval could not be found nor a discussion of how gender may confound the results).

The sponsor was asked to provide more information addressing the potential role of pre-existing concomitant cardiovascular disorders and medications. The sponsor replied in a N005 submission explaining that few subjects were receiving medications that they identified as potentially QT prolonging co-medications: sertraline hydrochloride, fluoxetine hydrochloride, haloperidol, risperidone. Only 1-2% of subjects used one of these medications and 6% of subject used any one of these medications. Also refer to a previous section showing the incidence of common (at least 5%) concomitant medications, noting that lorazepam, zolpidem and related drugs were most commonly used, as well as the anticholingergic agent benztropine mesilate. In the opinion of the undersigned, it is difficult to extrapolate a potential drug-drug interaction effect on QT or other cardiovascular or ECG effects from the data of Study -1009.

The sponsor also provided upon request information on concomitant conditions. Treatment groups showed small group differences on the incidence of pre-existing cardiac conditions (17% of paliperidone subjects compared to 22% of the moxifloxacin subjects). Upon request the sponsor provided a listing of these cardiovascular conditions (a copy of this list was previously provided in this subsection of this review). In the opinion of the undersigned, it is difficult to extrapolate a potential drug-cardiovascular interaction effect from results of Study -1009. As previously summarized, the most common cardiovascular condition was hypertension with a few subjects showing heart rate abnormalities (e.g. intermittent bradycardia or rapid pulse, each in 1 subject) or ECG abnormalities (e.g. first degree AV block in 1 subject, T wave abnormality in another subject). See the final section of this review for further comment and recommendations on the need to better characterize potential drug-drug and drug-disorder interactions effects.

Finally, another consideration with respect to interpreting results on the PK-PD relationship is that QT interval may be more strongly influenced by the rate of increase in plasma concentrations rather than on the absolute levels. A discussion or analyses of data with respect to the rate of increase in plasma levels against QT interval changes over time, cannot be found in the CSR. Although a comment is found in the CSR (page 70) in which it is suggested that smaller effects on QT interval may be "observed when plasma concentrations increase less rapidly, because there is more time for physiological adaptation."

Results of Other ECG Parameters

The following summarizes the incidence of outliers on ECG parameters.

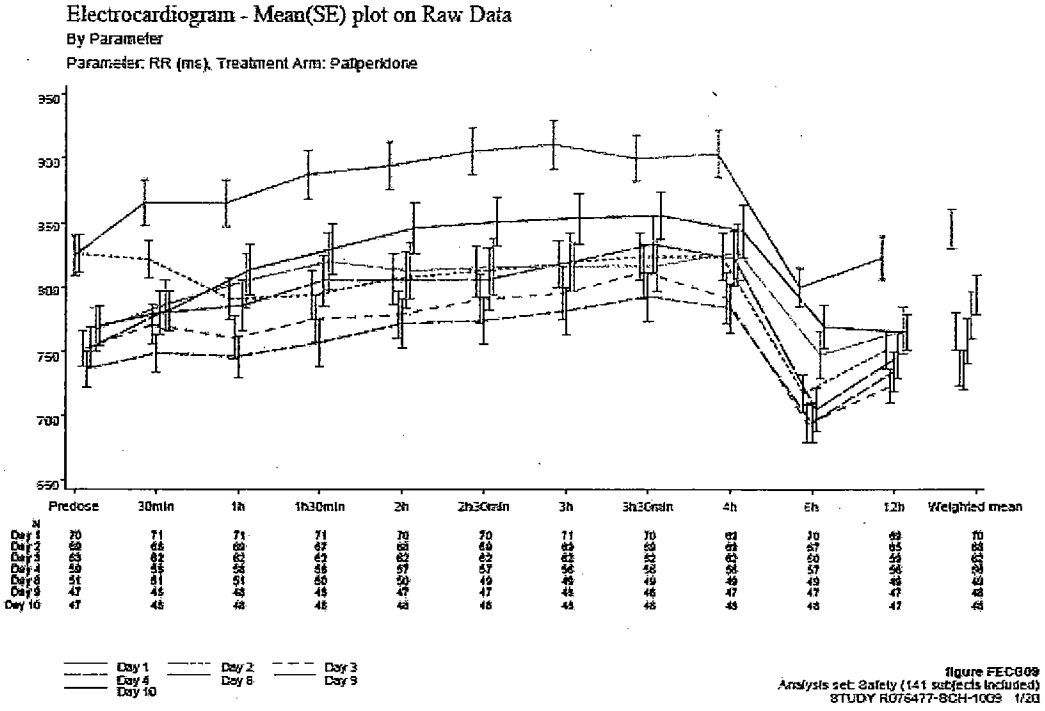
Table 18:Number of Subjects With Potentially Clinically Important Treatment-Emergent ECG Values (Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)		Placebo/Moxifloxacin (N=69)	
	n	(%)	n	(%)
Heart Rate				
> 100 bpm	26	(36)	6	(9)
< 55 bpm	18	(25)	24	(35)
QRS Interval				
> 120 ms	0		1	(1)
PR Interval				
> 200 ms	7	(10)	9	(13)
< 120 ms	4	(6)	6	(9)

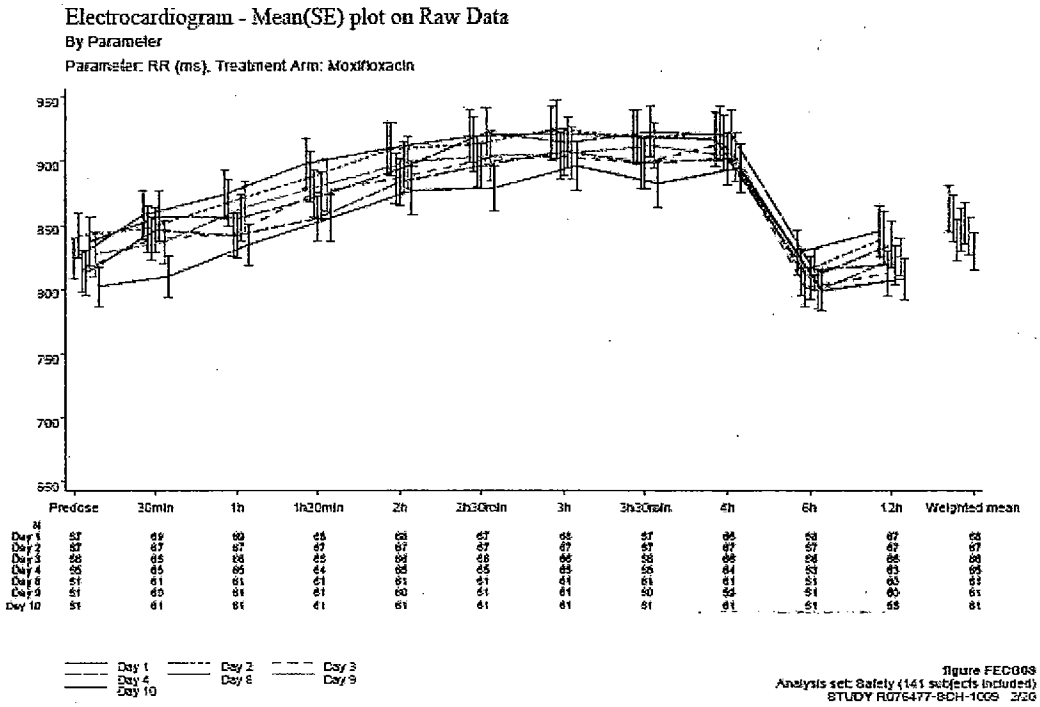
Cross-reference: Attachment 5.1

A graphical representation of study results on raw mean RR for each study day over time is shown below (with a color coded legend for each study day).

Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



A similar graphical representation for HR was previously provided in this review.

Reviewer Comments on Effects of Pal versus Moxiflaxicon Effects on PR Interval. *PR interval values generally showed decreases during treatment days compared to non-treatment days in Paliperidone, while moxifloxacin treated subjects showed not clear PR interval drug effect, as shown in the following tables. It does not appear that the differences between the treatment groups on PR interval effects cannot be accounted for by differential drug effects on HR changes over time or by study day, since the treatment groups appeared to show similar mean increases in HR at similar treatment time-points (see figures of HR, shown previously in this review).*

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Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time

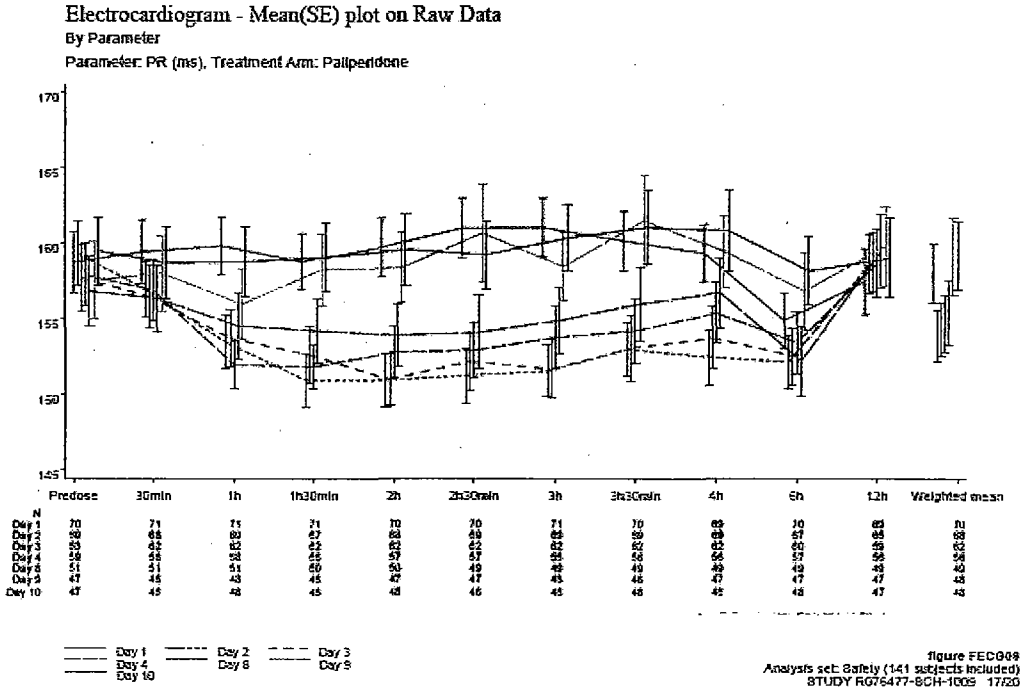

figure FECG09
Analysis set: Safety (141 subjects included)
STUDY RG76477-SCH-1009 17/20

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Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time

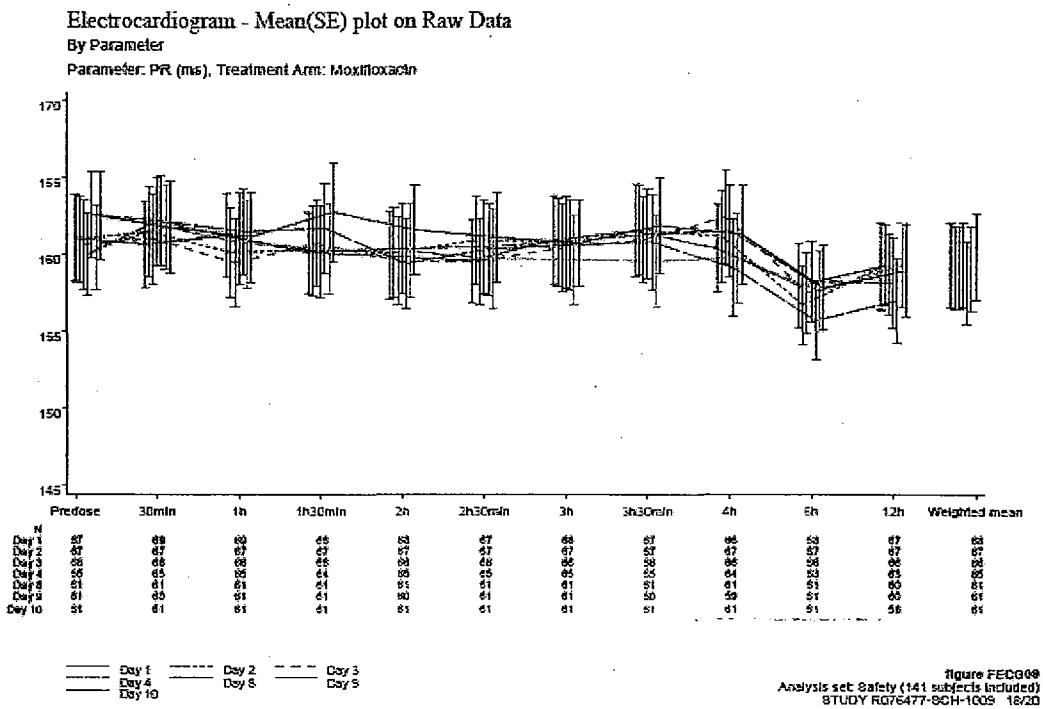


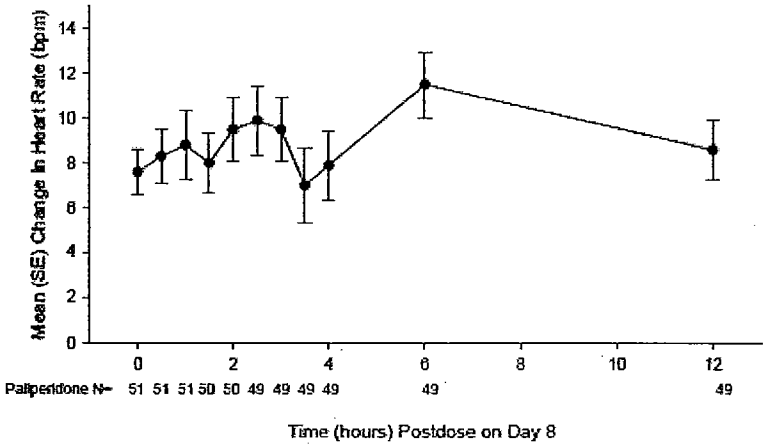
figure FECG09
Analysis set: Safety (141 subjects included)
STUDY R076477-SCH-1009 18/20

Table 20: Number of Subjects With Treatment-Emergent Changes in T- and U-Wave Morphology
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)		Placebo/ Moxifloxacin (N=69)	
	n	(%)	n	(%)
T Wave				
Low T Waves	14	(19)	10	(14)
Diphasic (Pos-Neg) T Waves	7	(10)	7	(10)
Flat T Waves	7	(10)	6	(9)
Diphasic (Neg-Pos) T Waves	5	(7)	6	(9)
Slightly Negative T Waves	5	(7)	9	(13)
Deeply Negative T Waves	1	(1)	2	(3)
Notched T Waves	1	(1)	1	(1)
Tall T Waves	0		3	(4)
U Wave				
Yes	2	(3)	1	(1)

Cross-Reference: Attachment 7.

Figure 8: Plot of Mean Change* in Heart Rate on Day 8 Matched Time Points
(Study R076477-SCH-1009: Safety Analysis Set)

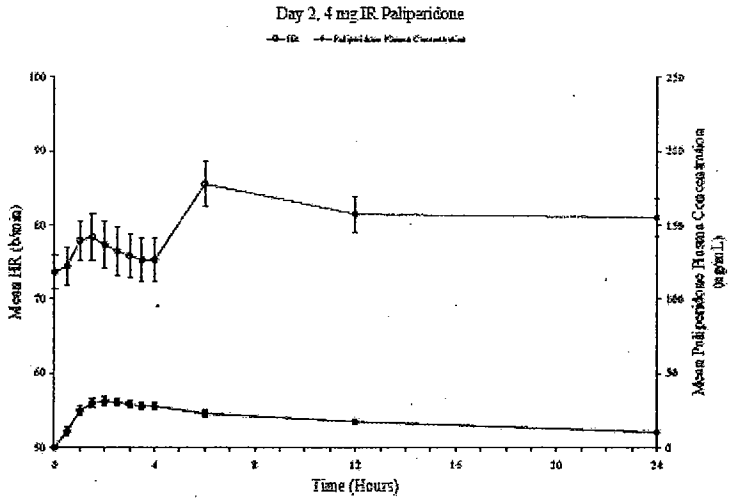


* Mean change from Day 1 (placebo) to Day 8 corresponding timepoints.

Cross-reference: Attachments 5.2.1 and 5.2.2.

The following figure illustrates mean Pal plasma levels with mean heart rate values over time.

Figure 9: Mean (90% CI) Paliperidone Plasma Concentrations and HR Profiles in Function of Time
(Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



Cross-reference: Attachment 6.3.

Reviewer Comment. *The sponsor notes that the initial peak increase in heart rate occurred near the anticipated Tmax and was most prominent after the first dose of Pal (a 4mg dose-level) compared to subsequent days of Pal treatment despite that daily dose-levels were increased on treatment Days 3 (given 6 mg) and 4 (given 8 mg). Heart rate increased again at the 6 hour post-dose assessment time-point which was also observed on the placebo treatment day (Day 1).*

The results suggest that perhaps initial exposure to Pal results in the greatest drug-induced change in heart rate, yet when examining results of day-averaged heart rate the mean change in heart (from Day 1 averaged heart rate values) showed evidence for greater effects with increasing dose-level over subsequent treatment days (mean changes of 7.8, 11.2 and 12.1 bpm on Day 2 at 4 mg, Day 3 at 6 mg and Day 4 at 8 mg, respectively). However, continued treatment at the 8 mg daily dose-level showed evidence for a decreasing Pal induced effect on increased heart rate over subsequent treatment days (Days 4 through 8) at this fixed daily dose-level (when comparing Days 4 and 8 on the day-averaged mean change from the day-averaged value on Day 1 the mean change was 12.1 and 7.3 bpm, respectively). However, it is important to note the large between subject variance on mean changes in heart rate such that this possible PK-PD relationship may not apply to all subjects. It is likely that other factors that influence heart rate affect Pal induced changes in heart rate (e.g. consider underlying diurnal changes in heart rate, among others).

Also note that the incidence of subjects with high PR values (10%) is numerical larger than the incidence of subjects with low PR values (6%) among the Pal subjects.

Vital Sign Results

The study did not include vital sign assessments during treatment, but only at baseline/screening and at the end of the study or upon early withdrawal. Therefore, results on vital sign parameters were unrevealing.

Serious Adverse Events

The following are SAEs observed following Pal treatment in the study:

- "Severe" dystonia was reported as an SAE on day 3 at approximately 4 hours post-dose of 6 mg IR Pal in subject 109043 which led to this subject withdrawing early from the study.

- Subject 109047 had "extrapyramidal disorder" and "dyspnea" ("severe dyspnea" with "neck spasms" and "swollen tongue") reported as SAEs that also led to early study withdrawal. These events occurred on Day 6 following the 6 mg Pal dose.

Adverse Dropouts

In addition to the above SAEs that were also ADOs, the following ADOs occurred after Pal treatment:

- Subject 109004 (limiting adverse event: hyperkinesia)
- Subject 109040 (limiting adverse events: dystonia, hypertonia),
- Subject 109093 (limiting adverse event: bradykinesia),
- Subject 109169 (limiting adverse event: tetany): this subject also had dizziness, tachycardia and other AEs along with "teteny and mild eye abnormality" on Day 2 after the 4 mg dose.

The following ADO involved abnormal ECG (non-specific T wave abnormalities) as described in the following (copied from the CSR):

Subject 109076 (limiting adverse events: tachycardia, abnormal ECG), a 42-year-old man with residual schizophrenia was receiving haloperidol for psychosis, clonazepam for anxiety, and benzatropine for prophylaxis of extrapyramidal symptoms before entering the study. His medical history included headaches, insomnia, anxiety, paranoia, and auditory hallucinations. Haloperidol was discontinued on Day -7 of the screening period. The subject was randomly assigned to the IR paliperidone treatment group. No adverse events were reported after administration of placebo on Day 1. On Day 2, after administration of 4 mg IR paliperidone, the subject's heart rate increased from a predose rate of 77 bpm to a maximum of 127 bpm at 6 hours postdose. The subject's heart rate was 99 bpm 12 hours postdose on Day 2. An adverse event of tachycardia was reported on Day 2. The investigator considered the tachycardia to be of moderate intensity and of probable relationship to study drug. No adverse events were reported on Day 3 after administration of 6 mg IR paliperidone, although low or negative T waves, (non-specific T wave abnormality) was noted on ECG. On Day 4, after administration of 8 mg IR paliperidone, it was reported as an adverse event of moderately severe ECG abnormality. ECG abnormality was considered by the investigator to be of probable relationship to study drug. The subject was discontinued from the study due to tachycardia and ECG abnormality; both events resolved within 2 days after discontinuation of study drug.

The Incidence of Potential Pro-Arrhythmic-related AEs

The following table shows the incidence of potential pro-arrhythmic AEs reported in the study using AE terms (including seizure, syncope, ventricular fibrillation and flutter, TdP, and adverse events consistent with sudden death), as recommended in the ICH E14 Guideline ("The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs").

Table 22: Incidence of Cardiovascular and Potentially Related Adverse Events (Study R076477-SCH-1009: Safety Analysis Set)

	Paliperidone Treatment Group[a]		Moxifloxacin Treatment Group[b]	
	Placebo	IR PAL	Placebo	Moxifloxacin
WHOART Body System	(Day 1)	(Days 2-10)	(Days 1-7)	(Day 8-10)
WHOART Preferred Term	(N=72)	(N=69)	(N=69)	(N=62)
Investigator Verbatim Terms	n (%)	n (%)	n (%)	n (%)
Body as a whole - general disorders				
Syncope	0	0	0	1 (1.6)
syncopal episode				

[a] The paliperidone treatment group received placebo on Day 1 and paliperidone on Days 2 through 8.

[b] The moxifloxacin treatment group received placebo on Days 1 through 7 and moxifloxacin on Day 8.

Cross-reference: Attachment 8.1.1.

Reviewer Comments.
See reviewer comments above, on results of PK and QT interval and the PK-PD relationship. Other study results generally failed to show any clinically remarkable new safety findings. Yet the study did not examine drug effects on vital signs that included assessments near Tmax or other on-treatment time-points.

One potentially notable observation was that one Pal subject (a 42 year old healthy patient) had non-specific T wave changes on Days 3 and 4 of treatment (corresponds to 6 mg and 8 mg treatment days, respectively) along with increased heart rate first observed on Day 2 (corresponds to the first day of Pal treatment in which a 4 mg dose was given). These events led to early study withdraw after the 8 mg treatment on Day 4. No other factors or explanations that would account for these adverse events could be found in the in-text description in the CSR on this subject (109076).

See final section of this review for further comments and recommendations.

B. A Phase I Study with Vital Sign and ECG Results at 24 and 48 Hours after 3mg or 6 mg of OROS Pal

Since Study SCH-1009 did not include vital sign results near Tmax the sponsor was asked to clarify if any Phase I study was conducted that included vital sign measures near Tmax. The sponsor replied in a 6/7/2006 response that a Phase I PK study, Study –P01-1005 included measures of Tmax. This study parallel group, placebo-controlled, double-blind Phase I study was conducted on generally healthy, 20-45 year old Japanese (N=24 of which 14 subjects were male and 10 were female) and Caucasian (N=24; of which 14 were male and 10 were female) subjects. The Japanese subjects had not lived outside of Japan for more than 5 years (and were born in Japan) and were normotensive prior to study entry (were within a specified normal BP range). All subjects had to have a BMI of 18-25 kg/m.^{2} The Caucasian subjects were sex, age (±10% of age by gender) and weight (±30% of weight by gender) matched to the Japanese subjects in the United Kingdom study.

Subjects received a SD of 3 mg of Pal (Day 1) followed by MDs of 3 mg Pal (daily) or placebo on Days 5-11, then on Day 19 subjects received a SD of 6 mg of Pal (all doses given in fasted conditions). Vital sign measures were conducted at screening, pre-dose (on Day 1), then at 24 hours and 48 hours post-dose after the first dose of 3 mg or placebo (study Days 2 and 3, respectively), then at these same post-dose time-points after the last MD of daily 3 mg Pal or placebo (at 24 and 48 hours post-dose on study Days 12 and 13). 24 and 48 hour post-dose assessments were conducted again after the 6 mg SD or placebo treatment (on study Days 20 and 21) and a final end-of study assessment (at 24 and 48 hours post-dose, corresponding to study Days

The sponsor concludes in their 6/7/06 response submission that at Tmax "no changes were observed for either systolic or diastolic blood pressure whereas slight increases in pulse were noted."

Reviewer Comments on Results.
The following results were observed by the undersigned reviewer on the basis of numerical comparisons using results shown in graphs provided in the 6/7/06 response from the sponsor.

When examining the sponsor's graphs provided in their response to our inquiry between treatment group and within group mean values (within each ethnic group) effects can be observed over time that appear to reflect a drug-effect given the timing of the observations relative to dosing and given the PK properties of ER OROS Pal. The results depicted graphically (later in this review) generally showed within-Pal-group mean changes from baseline/predose values (or trends for changes) on various vital sign parameters (specified below) on at least the following assessment time-points: 24 hours after the first dose of 3 mg (corresponds to "c" time-point on the x-axis of the sponsor's figures) and 24 hours after the 6 mg SD treatment (corresponds to the "g" time-point on the x-axis of the sponsor's figures) which is near the anticipated Tmax (compared to the group mean baseline values and values at other assessment time-points). The following summarizes these observations:

- *Treatment group effects were generally observed (between placebo and Pal groups within each ethnic group). Orthostatic changes in HR and BP were generally observed in Pal groups near Tmax (and in some cases at additional post-dose time-points), while the placebo group generally showed little to no change or changes at these time-points.*
- *The "Asian" group appeared to show greater orthostatic changes or group differences in heart rate and blood pressure, than observed in the "White" group. As described later postural dizziness was more commonly reported in the "Asian" Pal group than in the "White" Pal group.*
- *The Asians generally showed greater Pal effects on mean supine systolic BP with treatment group differences of up to approximately 16 mmHg, but results are complicated by fluctuations in this parameter in the placebo group and it is not clear if they are reproduceable. Furthermore, the "white" group results are more difficult to interpret since Pal subjects had a group mean value than placebo subjects prior to treatment on this parameter.*

Supine heart rate generally showed little to no change or minimal treatment group differences (between Pal and placebo groups within each ethnic group).

It is notable that after MD treatment group mean differences on heart rate shows a similar peak effect near Tmax after the first dose of 3 mg to that observed after the last dose of the MD treatment regimen of 3 mg/day (based on numerical comparisons). This observation suggests little to no physiological adjustment or compensation to Pal-induced increases in orthostatic heart rate, similar to that observed for standing systolic BP results described above.

Final Comments on Results Showing Pal Effects

There are several problems with this Phase I study with respect to revealing a potential drug effect on vital signs. Greater Pal effects were observed in the Japanese group compared to the Caucasian group for at least orthostatic vital sign Pal effects that are also consistent with a greater incidence of AEs of postural dizziness, described later in the Japanese Pal group compared to the Caucasian pal group (29% and 13%, respectively). Yet PK properties generally showed similar results in these ethnic groups, as shown later.

The results on supine BP and orthostatic measures could at least in part be reflecting a blood sampling effect, but this potential confounding variable would not explain the time-dependent and treatment group (Pal versus placebo group) effects that appear to exist (based on numerical comparisons) that are previously described in this review. Moreover, the potential confound of blood sampling cannot explain ethnic group differences on orthostatic measures.

Comments on QTcF interval Results

This Phase I study did not show any remarkable changes in QTcF, based on results in graphs provided in the 6/7/06 response submission (also see selected graphs below).

Selected Graphs Provided in the 6/7/06 Response Submission

The figures shown below were provided by the sponsor in which the legend of the graphical displays are as follows in which subjects received a treatment sequence of 3 mg SD, 3 mg MD (Days 1-11, as below), then 6 mg SD on Day 20 (the below legend is copied from their response):

(a) Screening,
(b) Day 1, immediately before first 3mg dose;
(c) Day 2, 24h after first 3mg dose;
(d) Day 3, 48h after first 3mg dose;
(e) Day 12, 24h after last multiple 3mg dose,
(f) Day 13, 48h after last multiple 3mg dose,
(g) Day 20, 24h after first 6mg dose,
(h) Day 21, 48h after first 6mg dose,
(i) End of study

The following outlines treatment found in the CSR of the original NDA submission:

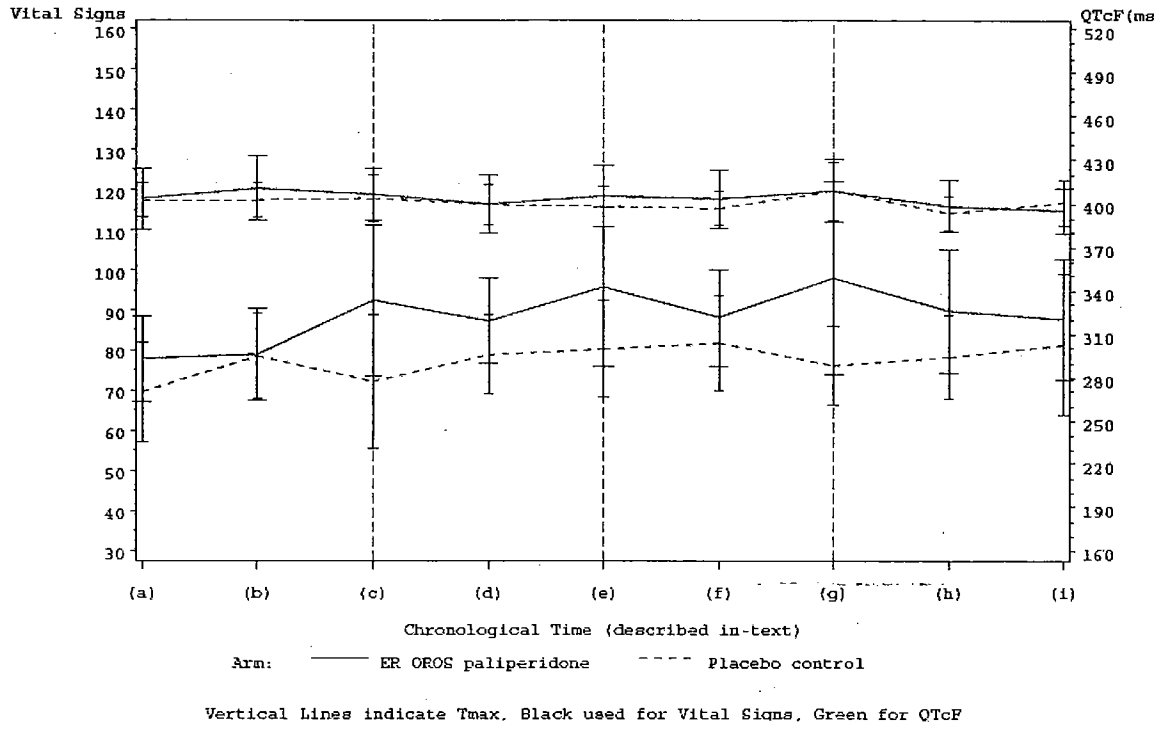
Table 1: Study Treatments

Day 1	Days 2-4	Days 5-11	Days 12-18	Day 19
SD of 3 mg ER OROS paliperidone or placebo	Washout	3 mg ER OROS paliperidone or placebo once daily for 7 days	Washout	SD of 6 mg ER OROS paliperidone or placebo

Cross-reference: Appendix 1.1

R076477—P01—1005: Mean+ —SD plots on Raw Data for Vital Signs Parameters and QTcF

Vital Signs Parameter=Pulse(bpm) when Standing+2m Race=ASIAN



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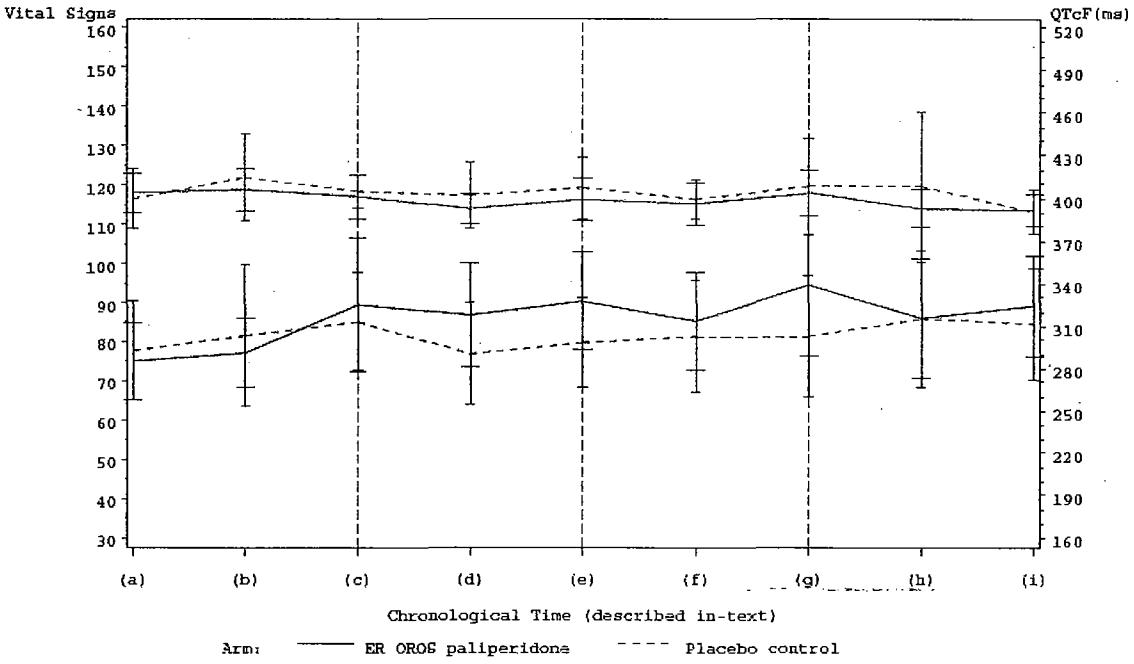
R076477-P01-1005: Mean+-SD plots on Raw Data for Vital Signs Parameters and QTcF

Vital Signs Parameter=Pulse(bpm) when Standing+3m Race=WHITE



Vertical Lines indicate Tmax. Black used for Vital Signs, Green for QTcF

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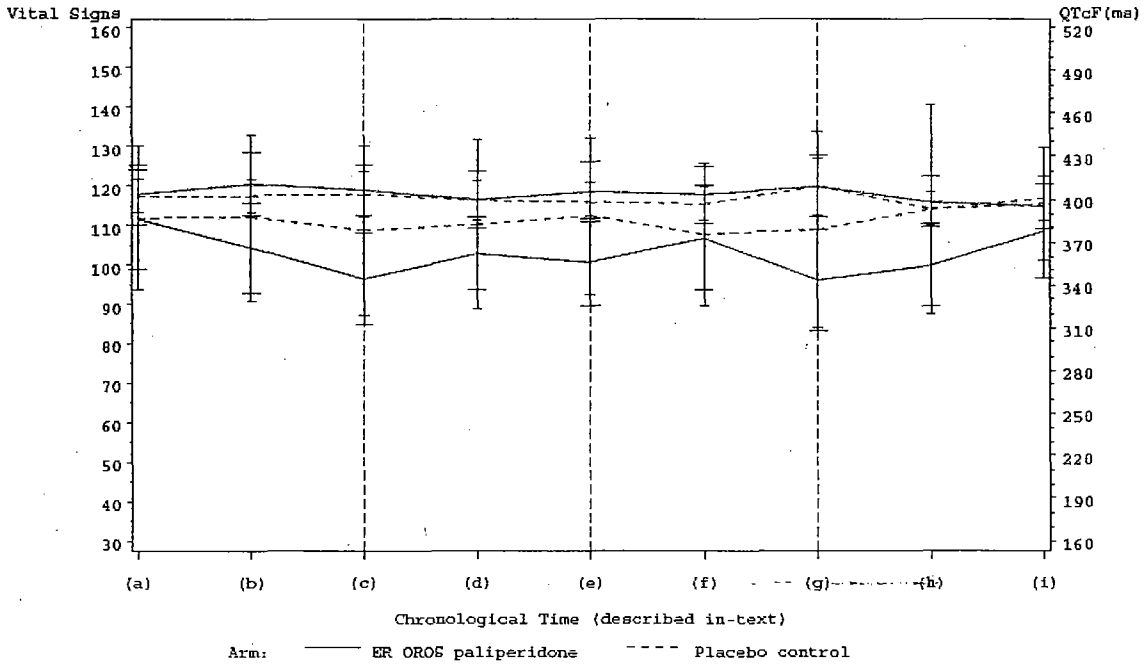
R076477—P01—1005: Mean+—SD plots on Raw Data for Vital Signs Parameters and QTcF

Vital Signs Parameter=SBP(mmHg) when Standing+2m Race=ASIAN



Vertical Lines indicate Tmax, Black used for Vital Signs, Green for QTcF

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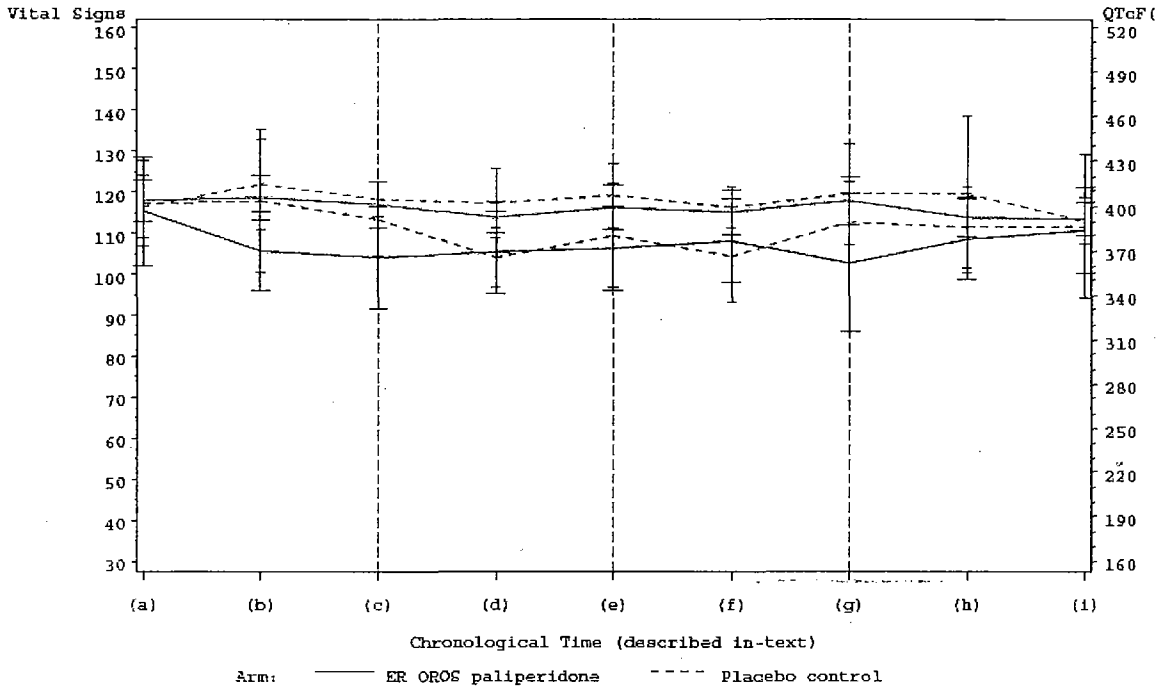
On Original

R076477-P01-1005: Mean+-SD plots on Raw Data for Vital Signs Parameters and QT

Vital Signs Parameter=SBP(mmHg) when Standing+2m Race=WHITE



Vertical Lines indicate Tmax, Black used for Vital Signs, Green for QTcF

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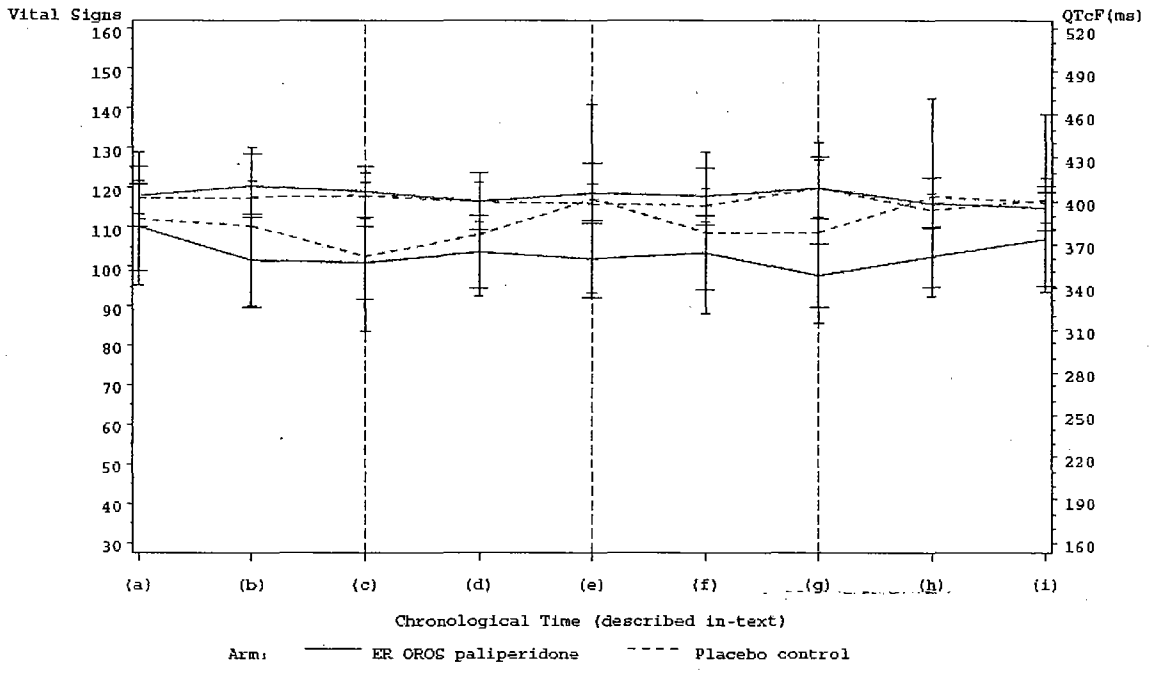
On Original

R076477-P01-1005: Mean+-SD plots on Raw Data for Vital Signs Parameters and QTcF

Vital Signs Parameter=SBP(mmHg) when Supine Race=ASIAN



Vertical Lines indicate Tmax, Black used for Vital Signs, Green for QTcF

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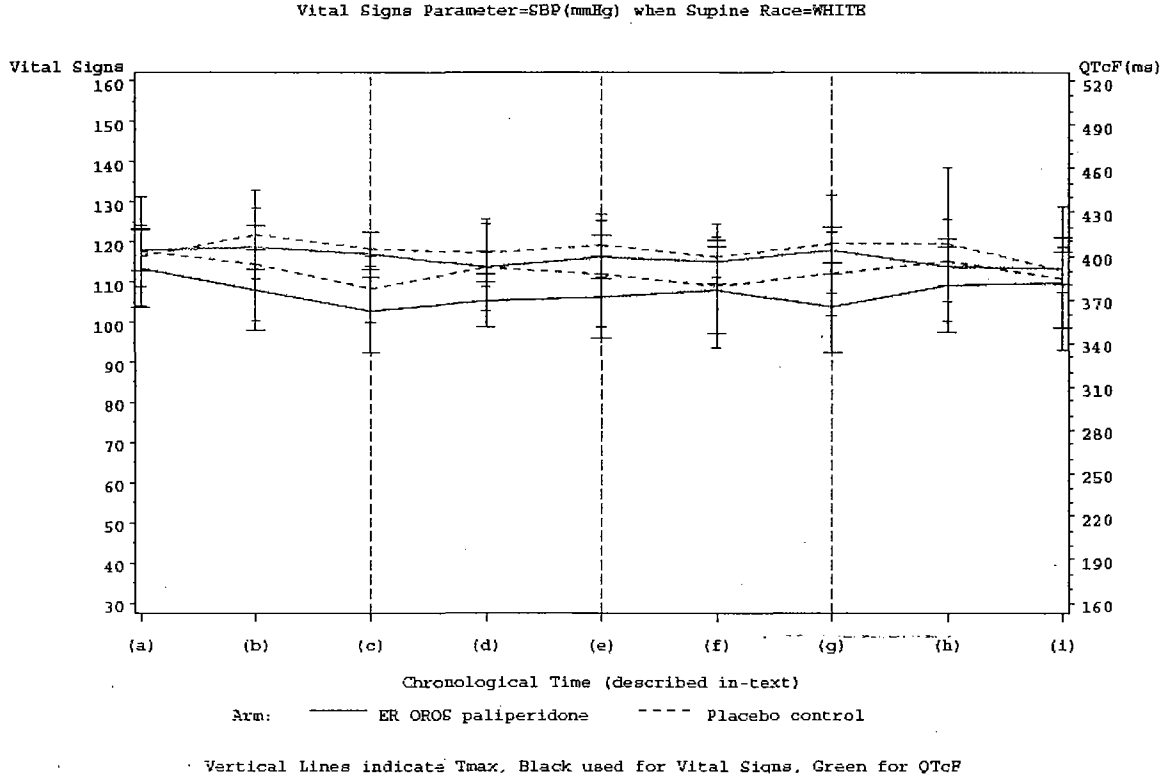
R076477-P01-1005: Mean+-SD plots on Raw Data for Vital Signs Parameters and QTcF



Note the table below shows comparable PK properties when comparing "Asian" to "white" subjects, yet the "asian" group had more AEs of postural dizziness than the "white" group following Pal treatment (29% compared to 13% in these groups, respectively).

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Table 1: Comparison of paliperidone plasma pharmacokinetic parameters of both ethnic groups

	Caucasian	Japanese	Japanese/ Caucasian ratio[1] (%)	90% CI (%)
3 mg SD data				
n	24	23	47	47
t_{max} (h)	25.02 ± 2.90	22.86 ± 4.27	-	-
C_{max} (ng/mL)	5.59 ± 2.84	6.60 ± 2.19	129.46	101.50 - 165.13
AUC_{0-24h} (ng.h/mL)	59.4 ± 27.4	79.9 ± 24.3	-	-
AUC_{∞} (ng.h/mL)	218 ± 114[2]	241 ± 84.2	118.70[5]	93.85 - 150.12[5]
$t_{1/2}$ (h)	20.8 ± 4.82[3]	19.6 ± 3.45[4]	-	-
CL/F (mL/min)	306 ± 194[2]	237 ± 97.2	-	-
3 mg MD data				
n	23	23	46	46
$C_{trough\ Day\ 11}$ (ng/mL)	11.0 ± 7.05	10.2 ± 4.12	-	-
$t_{max,ss}$ (h)	13.14 ± 8.92	14.26 ± 9.38	-	-
$C_{max,ss}$ (ng/mL)	12.5 ± 7.05	11.8 ± 3.95	102.56	82.63 - 127.30
$C_{avg,ss}$ (ng/mL)	10.1 ± 5.82	9.60 ± 3.26	-	-
$AUC_{0-24,ss}$ (ng.h/mL)	243 ± 140	230 ± 78.2	101.97	82.46 - 126.11
FI (%)	45.8 ± 18.4	42.5 ± 12.6	-	-
$t_{1/2}$ (h)	27.6 ± 4.20	25.4 ± 3.51	-	-
CL/F (mL/min)	265 ± 128	242 ± 80.8	-	-
6 mg SD data				
n	24	23	47	47
t_{max} (h)	23.80 ± 1.94	22.89 ± 3.76	-	-
C_{max} (ng/mL)	12.7 ± 6.19	13.8 ± 8.22	105.37	82.92 - 133.89
AUC_{0-24h} (ng.h/mL)	142 ± 57.8	173 ± 87.6	-	-
AUC_{∞} (ng.h/mL)	513 ± 256	565 ± 368[2]	109.80[5]	86.92 - 138.69[5]
$t_{1/2}$ (h)	23.6 ± 3.74	22.9 ± 6.48	-	-
CL/F (mL/min)	246 ± 132	216 ± 78.6[2]	-	-

[1] The presented ratio is calculated as the geometric mean. Ratio and CI are constructed on log-scale and backtransformed. [2] n=22. [3] n=23. [4] n=24. [5] n=46.

C. Vital sign and Safety Related Results from a Food Effect Phase I Studies P01-1008 and P01-1012 with Vital Sign Assessments Conducted hourly Post-dose

The following was also provided in Section 7.1.8.3.1 of this review but is copied below for the convenience of the reader and since it relates to the topic of cardiovascular effects near Tmax, discussed in previous sections.

Caveat on Phase III results on BP and Timing of Assessments Relative to Dose, PK and other Potential Time-dependent Confounding Variable and Relative to Fed Versus Fasted Conditions.

The sponsor was asked to provide data for vital sign results near Tmax ideally from a schizophrenia trial but the Phase III trials and the QT prolongation study, Trial –SCH-1009 did not include assessments at multiple time-points in order to enhance capturing Tmax or other time-dependent confounding variables. Study -1009 only included baseline and end-of-study vital sign assessments (this study is described under Section 7.1.12). The sponsor provided results of Study SCH-1009 in response to this inquiry which is described in the previous

subsection of this section (Section 7.1.13 B) but had a limited number of subjects and used 3 and 6 mg dose-levels. Also vital signs were only conducted at pre-dose, 24 and 48 hour post-dose time-points on selected treatment days.

It is first notable that both food effect studies did not include ECG assessments during study drug exposure (end-of-study and screening assessments were conducted).

P01-1008 SD 15 mg Pal (and Phase III formulations) Food Effect study (in bed for up to 36 hours post-dose).

The undersigned found results of Study P01-1008 in the N000 submission that had vital sign assessments hourly over 36 hours with some additional time-points thereafter at 48, 72 and 96 hours post-dose. This study used the 15 mg Phase III formulation in fasted state, 15 mg in fasted state and 15 mg fed state which should the following results on supine BP:

- *Increase BP (from predose values) occurred in all groups starting near 29 or 30 hours post-dose in under each fasted treatment condition and near 25 hours post-dose in the fed condition that appeared to peak at 36 hours (but possibly later since the next assessment did not occur until 48 hours post-dose) in each of the fasted conditions and in the fed condition.*
- *The maximum mean increase in BP (systolic) observed at 36 hours was highest in the fed- condition (13.5 mmHg), next highest in the fasted condition (9.9 mmHg) and lowest in the Phase III fasted condition (7.3 mmHg).*
- *Peak BP increases may be in part be reflecting the time-point upon which subjects were not longer required to be in bed (following their 36 hour PK sampling). Yet, differences were observed between treatment conditions with the fed state being associated with the greatest increase in BP. Maximum mean increase in sBP may be even greater than the above values since the above values were found in the last hourly vital sign assessment (at 36 hours-post-dose) while the next hourly assessment did not occur until 48hours post-dose with little to no change in BP observed at this time-point.*
- *Given the above findings it is critical to note that subjects were to remain in bed through the 36 hour time-point (for blood sampling) and subjects received lunch at 4 hours PK sampling). Dosing was given in the morning.*
- *Group mean decreases occurred in all 3 treatment conditions at most time-points during the first 24 hours or longer after dosing with the greatest decreases occurring in the Phase III fasted condition..*

Only selected sections of this CSR was reviewed (SAEs, ADOs, Attachment 5.1 on vital sign results and other selected sections).

The following table shows the results discussed above (taken from Attachment 5.1 in the CSR of this Phase I study).

STUDY JJPRD R076477-P01-1009

Output DVS.01: Vital Signs - Descriptive Statistics (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	Change N	Change Mean	Change SE	Change SD	Change Med	Change Min	Change Max
Supine SBP(mmHg)														
SCREENING														
Screening	90	123.0	9.58	123.5	103	140								
PH3 FASTED														
Predose	66	117.4	9.28	116.0	100	141								
1H	66	113.6	10.23	114.0	89	143	117.4	66	-3.8	1.09	8.85	-3.5	-33	29
2H	66	113.9	9.44	113.5	92	142	117.4	66	-3.5	0.99	8.06	-4.0	-31	16
3H	66	114.9	9.26	114.0	96	138	117.1	65	-2.6	1.07	8.60	-1.0	-22	12
4H	66	114.0	8.79	113.5	99	136	117.4	66	-3.3	1.04	8.43	-4.0	-30	15
5H	66	116.8	9.15	116.0	99	142	117.4	66	-0.5	1.06	8.63	-1.0	-21	19
6H	66	114.1	9.83	113.0	94	140	117.4	66	-3.3	1.16	9.41	-2.0	-27	21
7H	66	110.1	9.76	110.0	90	154	117.4	66	-7.2	1.25	10.16	-7.5	-29	27
8H	66	108.7	8.52	108.0	91	140	117.4	66	-8.6	1.14	9.30	-9.5	-29	20
9H	66	108.6	8.70	107.0	93	139	117.3	65	-8.9	1.12	9.05	-9.0	-33	12
10H	66	110.6	10.05	108.5	94	154	117.4	66	-6.7	1.26	10.22	-7.0	-25	27
11H	66	113.3	9.55	112.0	97	130	117.4	66	-4.1	0.99	8.01	-4.0	-24	13
12H	66	113.6	8.99	114.0	94	136	117.4	66	-3.8	1.22	9.89	-3.0	-27	19
13H	66	110.4	7.89	109.0	97	132	117.1	65	-6.9	1.02	8.22	-6.0	-28	12
14H	66	111.5	11.21	109.0	92	140	117.4	66	-5.9	1.15	9.31	-5.5	-30	22
15H	66	109.0	7.85	110.0	90	129	117.4	66	-8.4	1.17	9.48	-8.0	-29	15
16H	66	108.7	7.70	108.0	93	127	117.4	66	-8.7	1.08	8.80	-7.5	-29	12
17H	66	107.5	7.95	107.0	89	128	117.4	66	-9.9	1.13	9.18	-8.0	-29	11
18H	66	108.1	8.63	107.0	84	128	117.4	66	-9.3	1.18	9.56	-9.0	-35	11
19H	66	109.1	10.46	107.0	87	138	117.4	66	-8.3	1.19	9.68	-8.0	-29	15
20H	66	109.7	8.83	111.0	92	131	117.4	66	-7.6	1.16	9.46	-9.0	-24	19
21H	66	108.9	8.56	109.0	87	129	117.4	66	-8.5	1.15	9.30	-8.0	-31	17
22H	66	110.0	9.10	109.0	92	127	117.4	66	-7.3	1.26	10.21	-7.0	-35	16
23H	66	109.9	9.46	110.0	77	127	117.4	66	-7.5	1.33	10.79	-7.0	-44	16
24H	66	113.5	8.97	112.0	97	139	117.4	66	-3.8	1.12	9.13	-4.0	-21	15
25H	66	116.8	8.68	117.0	96	137	117.4	66	-0.6	1.08	8.76	-0.5	-19	18
26H	66	118.3	10.23	118.5	97	143	117.4	66	1.0	1.28	10.36	2.0	-22	23
27H	66	116.9	10.37	116.0	94	150	117.4	66	-0.6	1.23	10.02	1.0	-23	29
28H	66	115.2	8.72	114.5	94	135	117.4	66	-2.1	1.13	9.21	-3.5	-22	21
29H	66	117.9	11.49	117.5	100	176	117.4	66	0.5	1.39	11.29	-1.0	-21	43
30H	66	117.7	11.04	117.5	99	154	117.4	66	0.3	1.28	10.41	-1.5	-26	22
31H	66	118.7	11.00	118.0	99	156	117.4	66	1.3	1.44	11.67	1.5	-27	24
32H	66	118.0	9.57	116.0	102	140	117.4	66	0.7	1.09	8.84	1.0	-29	20
33H	66	118.1	9.38	118.0	101	143	117.4	66	0.8	1.16	9.41	1.0	-27	25
34H	66	121.4	9.43	121.5	104	152	117.4	66	4.1	1.14	9.25	3.5	-23	31
35H	66	121.7	10.15	121.0	105	160	117.4	66	4.3	1.20	9.72	4.0	-20	39
36H	66	124.7	10.78	124.0	103	157	117.4	66	7.3	1.20	9.72	7.0	-15	36
48H	66	116.5	9.44	116.0	98	141	117.4	66	-0.8	1.12	9.09	-1.5	-22	25
72H	66	118.7	9.85	117.5	99	148	117.4	66	1.3	1.02	8.25	1.0	-22	18
96H	66	120.3	9.69	118.0	98	141	117.4	66	2.9	1.12	9.11	3.0	-15	26
FASTED														
Predose	63	116.2	7.80	114.0	104	134								
1H	63	112.8	8.91	112.0	93	143	116.2	63	-3.4	1.19	9.33	-5.0	-29	23
2H	63	114.5	10.01	114.0	95	143	116.2	63	-1.8	1.44	11.41	-3.0	-22	33
3H	63	114.4	8.90	115.0	93	133	116.2	63	-1.9	1.19	9.44	-3.0	-20	22
4H	63	114.7	9.51	115.0	94	140	116.2	63	-1.5	1.04	8.25	-1.0	-18	24
5H	63	115.7	7.56	116.0	97	134	116.3	62	-0.6	1.20	9.48	0.5	-28	23
6H	63	114.0	8.02	113.0	93	133	116.4	62	-2.7	1.22	9.64	-3.0	-32	18
7H	63	108.9	8.73	108.0	89	134	116.2	63	-7.4	1.18	9.33	-7.0	-32	12
8H	63	108.0	10.33	106.0	85	141	116.2	63	-8.3	1.30	10.33	-8.0	-30	19
9H	63	108.5	9.98	107.0	79	134	116.2	63	-7.8	1.34	10.60	-7.0	-34	27
10H	63	110.6	9.38	110.0	85	137	116.1	62	-5.8	1.13	8.89	-5.5	-27	15
11H	63	113.5	10.91	112.0	90	146	116.2	63	-2.7	1.31	10.39	-4.0	-26	27
12H	63	112.8	9.91	112.0	93	135	116.2	63	-3.4	1.29	10.23	-2.0	-25	23
13H	63	111.6	9.87	112.0	90	140	116.2	63	-4.7	1.39	10.94	-7.0	-24	35
14H	63	110.3	9.26	111.0	87	127	116.3	62	-5.9	1.14	8.97	-5.5	-24	17
15H	63	109.7	10.75	110.0	84	129	116.2	63	-6.5	1.28	10.17	-7.0	-27	18
16H	63	109.0	9.38	109.0	90	130	116.2	63	-7.3	1.15	9.09	-7.0	-22	16
17H	63	108.4	10.21	109.0	90	134	116.2	63	-7.9	1.12	8.89	-8.0	-27	11

18H	63	110.2	10.11	110.0	88	134	116.2	63	-6.0	1.21	9.62	-6.0	-26	15
19H	63	110.2	9.95	110.0	94	141	116.2	63	-6.0	1.18	9.38	-6.0	-29	23
20H	63	109.2	9.15	110.0	93	131	116.2	63	-7.0	1.09	8.64	-8.0	-27	14
21H	63	110.4	9.92	110.0	89	134	116.2	63	-5.9	1.23	9.78	-6.0	-33	15
22H	63	111.7	11.55	110.0	93	164	116.2	63	-4.5	1.69	13.32	-6.0	-30	57
23H	63	110.6	7.87	109.0	96	129	116.2	63	-5.7	1.21	9.60	-5.0	-30	22
24H	63	113.7	10.75	114.0	90	157	116.2	63	-2.6	1.47	11.64	-4.0	-38	28
25H	63	117.0	8.71	117.0	94	138	116.2	63	0.8	1.30	10.28	1.0	-31	30
26H	63	117.5	11.23	117.0	94	147	116.2	63	1.2	1.54	12.19	2.0	-31	29
27H	63	115.4	9.96	115.0	97	145	116.2	63	-0.9	1.16	9.19	0.0	-18	19
28H	63	115.1	9.66	114.0	94	144	116.2	63	-1.2	1.13	8.97	0.0	-20	20
29H	63	115.7	9.71	115.0	95	135	116.2	63	-0.5	1.13	8.93	-1.0	-18	21
30H	62	118.8	11.71	117.0	94	165	116.1	62	2.7	1.30	10.26	1.5	-15	36
31H	63	118.3	9.23	118.0	101	142	116.2	63	2.1	1.08	8.55	3.0	-19	18
32H	63	117.7	10.22	117.0	96	140	116.2	63	1.5	1.15	9.09	2.0	-23	24
33H	63	120.1	9.33	120.0	99	142	116.2	63	3.9	1.09	8.66	4.0	-16	26
34H	63	122.5	10.59	121.0	101	153	116.2	63	6.2	1.20	9.52	7.0	-18	29
35H	63	122.9	10.93	123.0	96	150	116.2	63	6.7	1.31	10.38	6.0	-22	39
36H	63	126.1	11.71	126.0	102	155	116.2	63	9.9	1.40	11.08	9.0	-16	45
48H	63	117.3	7.73	117.0	99	134	116.2	63	1.1	1.00	7.93	0.0	-20	22
72H	63	118.6	11.31	118.0	102	157	116.2	63	2.4	1.35	10.74	2.0	-16	33
96H	63	117.8	10.21	114.0	101	145	116.2	63	1.5	1.11	8.81	1.0	-18	25
[redacted] FED														
Predose	72	115.5	7.93	114.0	101	138								
1H	72	116.2	10.11	116.5	95	156	115.5	72	0.7	0.94	8.00	1.0	-15	30
2H	72	114.7	11.04	115.0	91	150	115.5	72	-0.8	1.20	10.21	0.0	-22	33
3H	72	112.8	8.60	112.0	94	133	115.5	72	-2.8	0.83	7.01	-2.0	-20	10
4H	72	116.1	10.15	115.5	94	152	115.5	72	0.5	0.91	7.71	1.0	-14	24
5H	72	118.4	9.45	118.0	100	142	115.5	72	2.9	1.08	9.17	1.5	-19	31
6H	72	116.5	10.39	116.0	99	144	115.5	72	0.9	1.09	9.27	0.0	-24	25
7H	72	111.8	8.55	112.0	86	135	115.5	72	-3.7	1.06	8.99	-4.0	-27	22
8H	72	110.4	8.03	109.0	95	132	115.5	72	-5.1	1.10	9.34	-4.5	-28	20
9H	72	110.5	9.00	110.5	90	137	115.5	72	-5.1	1.07	9.10	-5.0	-36	18
[redacted] FED														
10H	72	111.2	9.79	111.5	86	134	115.5	71	-4.4	1.28	10.75	-6.0	-44	22
11H	72	115.0	8.76	115.0	97	145	115.5	72	-0.5	1.04	8.84	-1.0	-24	33
12H	72	114.7	11.10	115.0	95	154	115.5	72	-0.8	1.38	11.67	-1.0	-31	40
13H	72	112.9	9.69	113.0	92	135	115.6	71	-2.5	1.13	9.49	-3.0	-29	31
14H	72	112.1	10.10	110.0	92	133	115.5	72	-3.5	1.19	10.11	-4.5	-28	20
15H	72	111.2	8.44	111.0	91	130	115.5	72	-4.4	1.10	9.36	-3.5	-25	16
16H	72	111.0	10.10	110.0	90	136	115.5	72	-4.5	1.36	11.55	-3.0	-34	27
17H	72	108.1	9.34	108.0	89	131	115.5	72	-7.4	1.18	9.99	-7.0	-30	19
18H	72	110.8	10.48	109.0	88	138	115.5	72	-4.7	1.16	9.88	-4.0	-26	18
19H	72	109.7	9.56	109.0	90	129	115.5	72	-5.8	1.15	9.79	-5.5	-28	17
20H	72	110.3	9.02	110.0	90	132	115.5	72	-5.3	1.11	9.44	-5.0	-23	19
21H	72	110.9	9.74	111.0	94	145	115.5	72	-4.6	1.15	9.79	-6.0	-20	31
22H	72	111.6	10.48	111.5	86	139	115.5	72	-3.9	1.34	11.40	-5.5	-28	25
23H	72	112.2	8.97	112.0	90	138	115.5	72	-3.4	1.22	10.37	-2.0	-25	22
24H	72	115.3	9.20	115.0	94	143	115.5	72	-0.2	1.09	9.21	0.0	-20	25
25H	72	118.6	11.10	117.0	95	150	115.5	72	3.1	1.29	10.99	2.5	-22	32
26H	72	118.3	10.90	115.5	99	150	115.5	72	2.8	1.39	11.77	1.0	-25	36
27H	72	116.1	9.37	115.0	96	147	115.5	72	0.5	1.28	10.84	-0.5	-24	27
28H	72	116.5	9.34	116.0	94	154	115.5	72	1.0	1.29	10.99	2.0	-20	42
29H	72	120.4	10.32	119.5	88	154	115.5	72	4.8	1.37	11.63	4.0	-23	42
30H	71	120.4	11.30	119.0	92	162	115.4	71	5.0	1.33	11.19	4.0	-27	50
31H	71	120.8	10.84	120.0	97	163	115.6	71	5.2	1.41	11.90	3.0	-22	51
32H	72	121.5	10.49	121.5	97	154	115.5	72	6.0	1.33	11.28	5.0	-17	42
33H	72	123.9	10.93	123.0	107	162	115.5	72	8.4	1.24	10.49	7.0	-20	42
34H	71	124.7	11.75	122.0	103	164	115.6	71	9.1	1.53	12.92	8.0	-18	52
35H	72	126.2	9.94	125.0	105	150	115.5	72	10.7	1.21	10.26	9.5	-15	38
36H	70	128.8	11.74	127.0	106	166	115.3	70	13.5	1.46	12.22	11.5	-12	48
48H	71	119.2	9.81	118.0	99	148	115.6	71	3.6	1.24	10.45	3.0	-23	31
72H	71	118.2	9.37	117.0	97	143	115.6	71	2.6	1.25	10.52	3.0	-19	32
96H	71	119.2	10.44	118.0	99	151	115.6	71	3.6	1.21	10.19	2.0	-18	33

Supine HR showed mean increases that appeared to coincide with the above mean BP increases as shown in the following (taken from Attachment 5.1 of the CSR):

STUDY JJPRD R076477-P01-1008

Output DVS.01: Vital Signs - Descriptive Statistics

Analysis Set: Safety

							Base	change					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
Supine pulse(/min)														

PH3 FASTED														
Predose	66	58.3	9.46	58.5	44	90								
1H	66	56.8	8.96	56.0	42	77	58.3	66	-1.5	0.93	7.52	-0.5	-33	11
2H	66	57.5	7.92	57.0	43	77	58.3	66	-0.8	1.09	8.74	0.0	-35	23
3H	65	56.2	7.59	56.0	43	78	58.6	64	-2.5	1.10	8.79	-2.0	-40	20
4H	66	58.1	8.23	58.0	42	87	58.3	66	-0.2	0.90	7.30	0.5	-18	24
5H	66	67.1	8.06	66.0	54	93	58.3	66	8.8	1.15	9.30	9.0	-11	37
6H	66	67.9	9.74	67.0	50	104	58.3	66	9.6	1.32	10.69	10.0	-20	35
7H	66	62.7	9.69	61.5	44	97	58.3	66	4.4	1.20	9.73	5.0	-20	28
8H	66	60.1	8.99	60.0	43	98	58.3	66	1.8	1.18	9.55	2.0	-30	29
9H	66	60.8	9.35	60.0	43	85	58.0	65	2.5	1.22	9.83	2.0	-27	37
10H	66	59.3	7.76	59.0	46	77	58.3	66	1.0	0.92	7.45	1.5	-19	17
11H	66	65.5	8.48	64.0	48	87	58.3	66	7.2	1.13	9.15	8.0	-23	36
12H	66	63.7	8.94	63.5	44	94	58.3	66	5.4	1.11	8.99	4.0	-22	25
13H	66	59.2	7.56	59.5	45	84	58.4	65	0.9	1.00	8.04	1.0	-25	28
14H	66	58.9	8.41	58.0	40	90	58.3	66	0.6	1.23	9.95	-1.0	-21	32
15H	66	57.3	8.90	57.0	40	96	58.3	66	-1.0	1.15	9.32	-0.5	-24	33
16H	66	55.6	9.14	54.0	40	89	58.3	66	-2.7	1.14	9.27	-2.5	-30	20
17H	66	55.8	8.95	55.5	38	84	58.3	66	-2.5	1.02	8.32	-3.0	-19	18
18H	66	56.8	10.17	55.5	40	86	58.3	66	-1.5	1.12	9.10	-2.0	-25	27
19H	66	56.2	9.14	55.5	40	86	58.3	66	-2.1	1.05	8.50	-2.5	-20	29
20H	66	57.3	11.08	56.5	39	100	58.3	66	-0.9	1.36	11.04	-1.5	-26	31
21H	66	56.8	9.25	57.0	40	99	58.3	66	-1.5	1.09	8.84	-1.0	-26	30
22H	66	56.9	10.15	56.0	37	97	58.3	66	-1.4	1.09	8.84	-1.5	-19	28
23H	66	59.7	9.66	58.0	41	97	58.3	66	1.4	1.24	10.04	0.0	-29	32
24H	66	66.0	13.67	64.5	43	123	58.3	66	7.7	1.62	13.15	7.0	-28	54
25H	66	68.7	11.19	67.0	49	111	58.3	66	10.4	1.21	9.81	10.0	-11	42
26H	66	73.5	11.76	70.0	54	117	58.3	66	15.2	1.27	10.31	15.0	-8	48
27H	66	70.0	11.66	69.0	50	117	58.3	66	11.7	1.30	10.54	10.0	-7	48
28H	66	69.8	12.54	68.0	49	113	58.3	66	11.5	1.68	13.68	9.0	-16	56
29H	66	75.3	13.29	73.5	55	130	58.3	66	17.0	1.71	13.87	15.0	-8	61
30H	66	74.8	12.41	74.0	53	122	58.3	66	16.5	1.49	12.12	15.0	-5	53
31H	66	73.2	11.44	74.0	50	119	58.3	66	14.9	1.42	11.50	15.0	-15	50
32H	66	69.0	13.09	68.0	50	127	58.3	66	10.7	1.57	12.77	9.0	-18	58
33H	66	67.2	11.65	65.0	51	115	58.3	66	8.9	1.35	10.94	8.0	-15	46
34H	66	65.7	11.38	65.0	45	111	58.3	66	7.4	1.42	11.50	7.5	-20	42
35H	66	72.7	12.11	72.0	54	113	58.3	66	14.4	1.42	11.51	13.0	-15	48
36H	66	75.7	11.51	75.0	56	116	58.3	66	17.4	1.39	11.21	16.0	-9	48
48H	66	66.2	10.05	66.0	45	99	58.3	66	7.9	1.23	9.96	7.5	-20	30
72H	66	64.2	9.22	63.0	46	96	58.3	66	5.9	1.09	8.80	7.0	-17	31
96H	66	64.7	9.51	64.5	42	87	58.3	66	6.4	1.24	10.07	7.5	-25	33
[redacted] FASTED														
Predose	63	58.6	11.50	57.0	42	110								
1H	63	55.9	8.60	54.0	40	80	58.6	63	-2.7	1.07	8.49	-1.0	-41	21
2H	63	58.0	10.14	57.0	43	85	58.6	63	-0.6	1.22	9.67	0.0	-28	36
3H	63	57.5	9.11	56.0	40	79	58.6	63	-1.1	1.11	8.80	0.0	-38	16
4H	63	59.7	8.79	59.0	41	80	58.6	63	1.0	1.21	9.62	2.0	-41	19
5H	63	66.4	10.33	64.0	51	105	58.6	62	7.8	1.16	9.12	8.0	-25	28
6H	63	68.5	9.93	68.0	50	95	58.7	62	9.5	1.22	9.62	11.0	-28	27
7H	63	62.5	9.37	61.0	44	100	58.6	63	3.9	1.18	9.33	5.0	-36	21
8H	63	59.2	9.14	60.0	41	102	58.6	63	0.6	1.32	10.48	2.0	-49	18
9H	63	59.2	8.99	60.0	42	90	58.6	63	0.6	1.13	9.00	1.0	-42	21
10H	63	60.3	9.07	59.0	46	88	58.6	62	1.7	1.08	8.48	3.0	-36	18
11H	63	66.6	10.55	64.0	51	100	58.6	63	8.0	1.10	8.76	9.0	-13	29
12H	63	64.9	10.74	62.0	50	103	58.6	63	6.3	1.09	8.66	7.0	-25	28
13H	63	61.2	10.08	60.0	43	90	58.6	63	2.6	1.05	8.32	4.0	-26	30
14H	63	58.3	10.26	57.0	43	95	58.7	62	-0.2	1.04	8.18	0.0	-23	27
15H	63	57.0	10.66	56.0	42	105	58.6	63	-1.6	1.30	10.32	-1.0	-22	52
16H	63	56.1	9.92	56.0	41	78	58.6	63	-2.5	1.12	8.88	-2.0	-32	18
17H	63	55.0	7.90	54.0	39	75	58.6	63	-3.6	1.06	8.41	-3.0	-37	12
18H	63	56.0	9.16	54.0	40	81	58.6	63	-2.6	1.12	8.86	-3.0	-31	22
19H	63	56.3	9.10	55.0	41	88	58.6	63	-2.3	0.93	7.42	-2.0	-33	22
20H	63	57.1	8.62	56.0	37	79	58.6	63	-1.5	1.16	9.20	-1.0	-40	23
21H	63	58.0	8.95	57.0	44	79	58.6	63	-0.6	1.03	8.18	0.0	-34	17
22H	63	59.3	10.77	58.0	40	101	58.6	63	0.7	1.06	8.44	0.0	-15	21

23H	63	59.2	9.59	59.0	41	84	59.6	63	0.6	1.02	8.06	2.0	-26	15
24H	63	66.1	12.28	64.0	45	100	59.6	63	7.5	1.55	12.33	7.0	-20	30
25H	63	70.3	11.73	69.0	49	108	59.6	63	11.7	1.30	10.29	12.0	-12	30
26H	63	73.5	11.61	71.0	50	107	59.6	63	14.9	1.46	11.56	15.0	-17	46
27H	63	70.4	13.42	68.0	47	124	59.6	63	11.8	1.34	10.64	11.0	-15	44
28H	63	68.2	11.20	66.0	50	108	59.6	63	9.6	1.12	8.89	10.0	-10	32
29H	63	73.2	12.01	71.0	56	119	59.6	63	14.6	1.31	10.40	13.0	-13	42
30H	62	74.5	10.73	74.0	54	109	59.5	62	16.0	1.34	10.51	17.0	-15	39
31H	63	71.8	11.10	71.0	51	104	59.6	63	13.2	1.26	10.02	13.0	-19	37
32H	63	68.0	10.68	67.0	44	106	59.6	63	9.3	1.07	8.48	9.0	-16	29
33H	63	66.4	10.40	66.0	48	96	59.6	63	7.8	1.17	9.31	7.0	-23	27
34H	63	65.1	10.12	63.0	48	97	59.6	63	6.5	1.08	8.54	7.0	-20	28
35H	63	72.7	11.08	72.0	54	116	59.6	63	14.1	1.07	8.49	14.0	-9	37
36H	63	77.0	10.63	78.0	54	104	59.6	63	18.4	1.31	10.41	19.0	-12	46
48H	63	66.6	9.40	67.0	45	92	59.6	63	8.0	1.32	10.44	10.0	-27	32
72H	63	64.7	9.25	64.0	44	94	59.6	63	6.1	1.17	9.32	6.0	-24	26
96H	63	63.8	9.64	64.0	42	86	59.6	63	5.2	1.49	11.81	7.0	-48	29
[redacted] FED														
Predose	72	58.8	9.70	58.0	40	98								
1H	72	66.3	9.63	66.0	50	95	58.8	72	7.5	0.86	7.26	7.0	-12	24
2H	72	65.6	10.45	65.0	44	100	58.8	72	6.7	0.91	7.74	6.0	-9	29
3H	72	62.1	8.65	61.0	45	88	58.8	72	3.3	0.87	7.35	3.0	-17	24
4H	72	63.0	9.26	62.0	42	93	58.8	72	4.1	0.86	7.27	4.0	-15	25
5H	72	66.9	9.67	66.0	48	100	58.8	72	8.0	0.87	7.36	8.0	-10	25
6H	72	66.9	10.61	64.5	45	99	58.8	72	8.0	1.04	8.83	7.0	-10	32
7H	72	62.9	9.95	62.0	42	91	58.8	72	4.1	0.90	7.63	4.0	-13	28
8H	72	62.2	9.63	62.0	43	92	58.8	72	3.3	1.19	10.02	3.5	-22	37
9H	72	61.0	9.53	60.0	46	92	58.8	72	2.1	1.04	8.79	1.0	-18	28
10H	72	62.1	10.29	62.0	42	100	58.8	71	3.2	1.00	8.43	3.0	-20	24
11H	72	66.3	10.23	65.5	43	99	58.8	72	7.5	0.94	8.00	7.0	-11	31
12H	72	66.8	10.45	67.0	45	99	58.8	72	8.0	1.01	8.57	7.0	-15	31
13H	72	62.4	10.81	60.5	41	105	58.8	71	3.6	1.19	10.04	2.0	-19	37
14H	72	60.3	8.93	59.0	46	94	58.8	72	1.4	0.99	8.31	2.0	-24	26
15H	72	58.7	10.36	57.0	43	90	58.8	72	-0.1	1.07	9.11	-1.0	-27	25
16H	72	59.3	10.67	58.5	41	109	58.8	72	0.5	1.25	10.59	0.5	-33	33
17H	72	57.1	9.31	57.0	40	87	58.8	72	-1.8	1.08	9.18	-2.0	-31	22
18H	72	57.4	8.34	57.0	42	88	58.8	72	-1.4	1.05	8.92	-1.0	-29	22
19H	72	58.7	10.15	58.0	42	96	58.8	72	-0.1	1.11	9.39	0.5	-39	27
20H	72	58.9	9.17	57.0	44	91	58.8	72	0.0	1.27	10.80	0.0	-38	29
21H	72	59.3	8.87	59.0	42	85	58.8	72	0.4	1.14	9.65	0.5	-33	29
22H	72	61.6	10.19	60.5	43	84	58.8	72	2.7	1.39	11.81	2.0	-32	37
23H	72	63.8	11.45	62.0	44	121	58.8	72	5.0	1.41	11.99	5.0	-32	45
24H	72	68.8	10.99	67.0	45	117	58.8	72	10.0	1.29	10.94	10.5	-13	41
25H	72	75.6	13.78	73.5	54	140	58.8	72	16.7	1.57	13.30	15.5	-14	91
26H	72	77.2	12.29	75.0	54	118	58.8	72	18.4	1.46	12.36	18.0	-12	46
27H	72	75.0	12.98	74.0	53	119	58.8	72	16.2	1.52	12.91	16.0	-5	50
28H	72	74.2	13.09	73.0	53	122	58.8	72	15.4	1.44	12.23	15.0	-8	46
29H	72	78.4	13.64	76.0	56	129	58.8	72	19.6	1.50	12.71	16.5	-1	61
30H	71	78.4	14.66	76.0	54	132	58.8	71	19.6	1.51	12.69	18.0	-3	64
31H	71	76.0	12.62	74.0	54	118	58.7	71	17.3	1.38	11.64	16.0	-6	51
32H	72	73.8	16.34	70.5	52	153	58.8	72	15.0	1.76	14.91	13.0	-7	95
33H	72	73.3	16.65	70.0	45	136	58.8	72	14.4	1.76	14.94	11.0	-11	70
34H	71	70.9	12.21	70.0	51	105	58.7	71	12.2	1.37	11.53	10.0	-7	48
35H	72	78.4	13.42	77.0	57	134	58.8	72	19.6	1.42	12.02	19.0	-1	66
36H	70	80.5	14.50	79.0	53	152	58.3	70	22.3	1.65	13.77	20.0	-3	84
48H	71	70.2	10.97	71.0	48	108	58.9	71	11.3	1.14	9.61	11.0	-12	40
72H	71	67.2	10.64	67.0	44	107	58.8	71	8.3	1.06	8.90	7.0	-14	29
96H	71	65.9	9.56	64.0	48	93	58.8	71	7.1	1.08	9.41	7.0	-15	23

It appears that the above study did not include orthostatic vital sign measures during treatment but reported AEs of orthostatic hypotension that were greatest in the 15 mg fed state compared to fasted [redacted] and fasted Phase III formulation conditions (7%, 5% and 2%) respectively. The most ADOs occurred in the

No SAEs or deaths occurred.

ADOs of dystonia were observed in a few subjects in the 15 mg Phase III fasted and 15 mg [redacted] fed conditions. One ADO due to tachycardia and dyspnea occurred in the fed [redacted] condition but not in the fasted conditions.

The most ADOs occurred in the 15 mg fed state as shown below (found in the CSR).

Table 10: Adverse Events Leading to Discontinuation of Treatment
(Study R076477-P01-1008: All Subjects Analysis Set)

Subj. nr. Age (Yrs) Race	Period Treatment Group	Body System Preferred Term Reported Term	Onset Time Duration	Outcome Action Taken Conmx Taken	Severity Relationship Serious
Treatment A: 15 mg ER OROS paliperidone Phase 3 formulation in fasted state					
100802	Period 2	Centr & periph nervous system disorders	1d 10:25	Resolved	Moderate
33	PH3	Dystonia	2:00	Permanent stop	Possible
White	FASTED	Acute dystonia		Yes	No
		Psychiatric disorders	1d 9:55	Resolved	Moderate
		Anxiety	4:30	Permanent stop	Possible
		Anxiety		No	No
100808	Period 1	Psychiatric disorders	2d 16:20	Resolved	Mild
32	PH3	Depression	0:30	Permanent stop	Probable
White	FASTED	Depression		No	No
		Psychiatric disorders	3d 16:20	Unknown	Moderate
		Depression		Permanent stop	Probable
		Depression		No	No
		Psychiatric disorders	2d 14:20	Resolved	Moderate
		Paranoid reaction	2:00	Permanent stop	Probable
		Paranoia		No	No
100819	Period 1	Centr & periph nervous system disorders	1d 4:49	Resolved	Moderate
26	PH3	Dystonia	0:36	Permanent stop	Probable
White	FASTED	Acute dystonia		Yes	No
100864	Period 1	Centr & periph nervous system disorders	1d 11:09	Resolved	Moderate
24	PH3	Dystonia	2:01	Permanent stop	Probable
White	FASTED	Acute dystonia		Yes	No
100875	Period 1	Psychiatric disorders	4d 7:45	Resolved	Moderate
21	PH3	Agitation	5d 20:00	Permanent stop	Possible
White	FASTED	Agitation		No	No
		Psychiatric disorders	4d 10:15	Resolved	Moderate
		Depression	5d 11:30	Permanent stop	Possible
		Depressed		No	No
		Psychiatric disorders	4d	Resolved	Moderate
		Somnolence	8d	Permanent stop	Possible
		Somnolance		No	No
Treatment B: 15 mg ER OROS paliperidone [redacted] formulation in fasted state					
100828	Period 1	Centr & periph nervous system disorders	6:30	Resolved	Moderate
23	[redacted]	Hyperkinesia	1d 5:45	Permanent stop	Probable
White	FASTED	Akathisia		Yes	No
100862	Period 3	Centr & periph nervous system disorders	13:45	Resolved	Moderate
29	[redacted]	Ptosis	10:05	Permanent stop	Probable
Black	FASTED	Ptosis		Yes	No
100851	Period 2	Respiratory system disorders	4d 23:40	Resolved	Moderate
29	[redacted]	Coughing	8d 13:00	Permanent stop	Doubtful
White	FASTED	Productive cough		Yes	No
		Respiratory system disorders	4d 23:40	Resolved	Moderate
		Pharyngitis	11d 3:45	Permanent stop	Doubtful
		Sore throat		Yes	No
		Skin and appendages disorders	4d 23:40	Resolved	Mild
		Sweating increased	8d 0:00	Permanent stop	Doubtful
		Night sweats		Yes	No

Treatment C: 15 mg ER OROS paliperidone [redacted] formulation after consumption of a high-fat breakfast					
100811	Period 1	Centr & periph nervous system disorders	1d 5:55	Resolved	Moderate
19	[redacted] FED	Dystonia	8:02	Permanent stop	Probable
White		Acute dystonia		Yes	No
100813	Period 1	Heart rate and rhythm disorders	1d 3:00	Resolved	Moderate
29	[redacted] FED	Tachycardia	1d 6:03	Permanent stop	Probable
Asian		Sinus tachycardia		Yes	No
		Respiratory system disorders	1d 6:55	Resolved	Moderate
		Dyspnoea	17:01	Permanent stop	Possible
		Dyspnoea		Yes	No
100816	Period 1	Centr & periph nervous system disorders	0:18	Persisting	Moderate
23	[redacted] FED	Headache	5d 1:42	Permanent stop	Possible
White		Headache		Yes	No
100824	Period 1	Centr & periph nervous system disorders	1d 1:55	Resolved	Moderate
27	[redacted] FED	Dizziness	8:55	Permanent stop	Possible
Asian		Dizziness		Yes	No
100859	Period 1	Respiratory system disorders	6d	Resolved	Moderate
24	[redacted] FED	Upper resp tract infection	4d	Permanent stop	Not related
White		Respiratory tract infection		Yes	No
100861	Period 1	Centr & periph nervous system disorders	1d 4:27	Resolved	Moderate
20	[redacted] FED	Dystonia	1:18	Permanent stop	Probable
White		Acute dystonia		Yes	No
100872	Period 1	Centr & periph nervous system disorders	1d 10:05	Resolved	Moderate
35	[redacted] FED	Dystonia	3:50	Permanent stop	Probable
Black		Acute dystonia		Yes	No
		Centr & periph nervous system disorders	1d 12:05	Resolved	Moderate
		Hyperkinesia	3:00	Permanent stop	Probable
		Akathisia		Yes	No
		Psychiatric disorders	2d 12:00	Resolved	Moderate
		Anxiety	18:05	Permanent stop	Possible
		Anxiety		No	No

Table 10: Adverse Events Leading to Discontinuation of Treatment (continued)
(Study R076477-P01-1008: All Subjects Analysis Set)

Note: One additional subject (100856) discontinued at the start of Period 2 due to adverse events he experienced in Period 1 with Treatment C. The adverse events he experienced in Period 1 were not of significant severity to warrant withdrawal of the subject by the investigator, but the subject was concerned and anxious that the adverse events could potentially be more severe in the following period and decided to discontinue from the study before proceeding to Period 2. The different adverse events the subject experienced during Period 1 are described in a narrative.

Cross-reference: Appendix 3.6.4

The above subject 100856 had postural hypotension, dystonia and other events that ultimately lead to an ADO in period 2.

AEs of tachycardia or palpitations were reported in 5 total subjects and were reported twice in some subjects such that: 4 of these AEs occurred in the fed contions, 2 of these AEs occurred in the fasted [redacted] condition and 2 AEs were reported in the fasted Phase III condition.

SD 12 mg Pal Food Effect, Postural Study (in bed versus ambulatory) P01-1012
Note that respiratory (nasal congestion), musculoskeletal (e.g. muscle spasm), vomiting and dizziness occurred in a larger incidence of subjects in the fed versus fasted conditions (coped from the CSR in the 120-Day SUR).

Table 9: Incidence of Common Treatment-Emergent Adverse Events by Body System and Preferred Term
(Study PALIOROS-P01-1012: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Fed Ambulant (Treatment A) (N=62) n (%)	Fasted Ambulant (Treatment B) (N=64) n (%)	Fasted Bed (Treatment C) (N=64) n (%)	Total (N=74) n (%)
Total no. subjects with adverse events	15 (24)	16 (25)	12 (19)	36 (49)
Nervous system disorders	10 (16)	9 (14)	9 (14)	24 (32)
Dizziness	7 (11)	5 (8)	3 (5)	12 (16)
Headache	2 (3)	4 (6)	5 (8)	9 (12)
Somnolence	2 (3)	1 (2)	1 (2)	4 (5)
Disturbance in attention	2 (3)	1 (2)	0	3 (4)
Gastrointestinal disorders	5 (8)	4 (6)	5 (8)	14 (19)
Nausea	2 (3)	2 (3)	1 (2)	5 (7)
Vomiting	3 (5)	0	1 (2)	4 (5)
General disorders and administration site conditions	4 (6)	1 (2)	2 (3)	7 (9)
Asthenia	0	0	2 (3)	2 (3)
Psychiatric disorders	1 (2)	4 (6)	2 (3)	7 (9)
Anxiety	0	2 (3)	0	2 (3)
Respiratory, thoracic and mediastinal disorders	4 (6)	1 (2)	3 (5)	7 (9)
Nasal congestion	3 (5)	0	2 (3)	4 (5)
Musculoskeletal and connective tissue disorders	3 (5)	1 (2)	2 (3)	6 (8)
Muscle spasms	2 (3)	0	0	2 (3)
Infections and infestations	0	2 (3)	0	2 (3)
Upper respiratory tract infection	0	2 (3)	0	2 (3)

NOTE: Incidence is based on the number of subjects, not the number of events
Only adverse events with an incidence of st least 2.5% in at least 1 treatment group are included.

There were no deaths or SAEs and only 3 ADOs of dystonic-related reactions in 2 subjects (1 in the fed and the other in the fasted state) and a respiratory system ADO (nasal congestion) in the fasted treatment condition.

The following additional safety findings are noted:

- "One subject (000027) experienced adverse events that included palpitations, heart rate increased, and blood pressure increased after receiving 12 mg ER OROS paliperidone in Treatment A (Attachment 3.1) (see Section 4.4.2.2). According to the vitals signs measurements, this subject experienced pulse rates above the normal range during the study

(maximum of 146 bpm 30 hours after study medication administration)." Treatment A is the fed condition.

The below table shows mean increases in heart rate that were greatest in the fed condition (from the CSR).

STUDY PALIOROS-P01-1012

Output DVS.01: Vital Signs: Descriptive Statistics on Raw Data and Change from Baseline

Analysis Set: Safety

							Base	change					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
Supine pulse(/min)														
SCREENING														
-	74	67.4	10.11	67.0	51	89								
FED AMBULANT														
Predose	62	60.2	6.75	59.0	51	79	60.2							
9H	62	65.0	9.35	62.5	52	89	60.2	62	4.7	1.12	8.85	3.0	-17	28
24h	58	64.7	10.01	62.0	51	98	60.2	58	4.4	1.19	9.10	3.5	-12	36
30H	58	79.1	13.49	78.0	58	146	60.2	58	18.8	1.80	13.69	19.0	-10	84
48h	58	70.9	11.80	68.0	52	121	60.2	58	10.6	1.42	10.79	10.0	-13	59
72h	57	72.6	12.11	71.0	52	110	60.3	57	12.4	1.57	11.87	14.0	-17	48
96h	58	68.0	11.27	65.0	52	107	60.2	58	7.8	1.40	10.65	6.0	-11	45
FASTED AMBULANT														
Predose	64	60.0	6.12	59.0	51	80	60.0							
9H	64	62.5	8.73	60.5	51	89	60.0	64	2.4	0.92	7.38	2.0	-19	18
24h	59	63.2	9.36	62.0	50	89	59.4	59	3.8	1.11	8.52	2.0	-20	30
30H	59	76.0	11.08	78.0	52	98	59.4	59	16.7	1.34	10.30	19.0	-6	39
48h	59	68.1	10.23	68.0	52	98	59.4	59	8.7	1.21	9.32	8.0	-5	37
72h	58	71.0	10.45	70.0	52	96	59.3	58	11.7	1.43	10.89	9.5	-15	43
96h	58	66.9	10.66	64.5	50	99	59.4	58	7.5	1.26	9.61	6.0	-16	37
FASTED BED														
Predose	64	60.7	7.65	59.0	51	79	60.7							
9H	64	64.5	9.76	62.5	50	86	60.7	64	3.8	1.17	9.39	3.0	-26	26
24h	62	63.7	9.32	61.0	51	85	60.6	62	3.1	1.27	9.99	2.0	-26	27
30H	62	77.5	10.50	79.0	53	112	60.6	62	16.9	1.66	13.06	17.0	-12	56
48h	61	69.4	10.21	69.0	50	89	60.6	61	8.8	1.41	11.04	9.0	-21	39
72h	60	69.6	9.00	69.0	48	94	60.7	60	8.9	1.25	9.65	9.0	-21	32
96h	60	68.2	9.49	68.0	51	96	60.7	60	7.5	1.34	10.41	7.5	-23	36

Supine SBP results are shown below.

Output DVS.01: Vital Signs: Descriptive Statistics on Raw Data and Change from Baseline (continued)

Analysis Set: Safety

							Base	Change					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
Supine SBP(mmHg)														
SCREENING														
-	74	118.1	8.72	118.5	100	136								
FED AMBULANT														
Predose	62	116.7	10.51	117.0	97	139	116.7							
9H	62	114.2	9.89	112.5	98	138	116.7	62	-2.5	1.29	10.15	-1.0	-29	28
24h	58	114.0	11.10	112.5	95	140	116.6	58	-2.7	1.55	11.82	-3.0	-33	29
30H	58	120.2	9.83	121.5	100	140	116.6	58	3.5	1.43	10.89	4.5	-23	26
48h	58	121.2	10.12	121.5	100	140	116.6	58	4.6	1.20	9.18	6.0	-15	29
72h	57	120.4	9.80	121.0	98	138	116.9	57	3.6	1.25	9.42	3.0	-23	27
96h	58	119.9	11.58	120.5	97	140	116.6	58	3.3	1.45	11.05	1.0	-18	42
FASTED AMBULANT														
Predose	64	115.4	11.05	113.5	92	138	115.4							
9H	64	109.9	9.95	107.5	96	136	115.4	64	-5.5	1.21	9.71	-6.0	-31	17
24h	59	113.6	11.56	112.0	91	139	115.6	59	-2.0	1.51	11.58	-2.0	-25	24
30H	59	119.5	10.97	118.0	99	139	115.6	59	3.8	1.43	11.01	3.0	-22	37
48h	59	119.4	9.63	118.0	98	139	115.6	59	3.8	1.14	8.78	4.0	-18	22
72h	58	118.8	9.83	119.0	94	139	115.9	58	2.9	1.36	10.37	2.5	-16	27
96h	58	118.0	9.24	119.5	98	139	115.7	58	2.3	1.25	9.52	3.0	-23	27
FASTED BED														
Predose	64	116.7	10.92	116.0	99	139	116.7							
9H	64	112.9	10.25	110.0	96	139	116.7	64	-3.8	1.30	10.42	-3.0	-38	21
24h	62	113.8	10.29	113.0	98	139	116.6	62	-2.8	1.32	10.37	-1.5	-30	23
30H	62	119.2	10.82	117.0	100	159	116.6	62	2.6	1.75	13.76	3.5	-38	60
48h	61	120.1	9.35	120.0	100	139	116.4	61	3.7	1.31	10.26	4.0	-20	30
72h	60	121.1	11.28	121.0	90	140	116.7	60	4.4	1.38	10.66	6.0	-26	25
96h	60	119.0	9.95	118.0	100	140	116.7	60	2.3	1.03	7.98	2.5	-17	16

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The submission does not include special safety trials. This drug class is not known to show withdrawal or abuse potential effects in Phase III trials (refer to labeling of approved drugs).

7.1.14 Human Reproduction and Pregnancy Data

The submission does not include special safety trials. The sponsor indicates that there were not pregnancies during any of the clinical trial.

7.1.15 Assessment of Effect on Growth

The submission does not include special safety studies.

7.1.16 Overdose Experience

The following is italicized since it contains some reviewer comments and conclusions by the undersigned reviewer (unless otherwise specified).

Section 7.1.18 on a review of the literature revealed overdose cases involving Ris that generally did not reveal any new findings that differ from that already described in this review. Note one

overdose subject had QT prolongation. See section 7.1.12 of a special QT interval study conducted with IR Pal.

Note some SAEs and/or ADOs of "overdose" or related events in Pal trials, as indicated in previous sections of this review. A description of any new remarkable findings that differ from that already described in other sections of this review. The SCS has a section focusing on overdose experience (section 6.5 in 2.7.4 of the submission). Overdoses occurring in the Phase III trials were reviewed by the sponsor and 3 subjects are described as having "excessive" overdoses of 24 g, 270 mg and an estimated overdose of 135 to 405 mg in each of these 3 subjects, respectively (numbers 300095, 300359 and 50215, respectively). Subject 50215 who had the highest estimated dose, was admitted to the hospital on the day of ingestion (exact times were not found in the sponsor's summary) with "prominent dysarthria" and a blood pressure of 100/60 mmHg. The subject was a 35 year old male. Subject 300359 (270 mg overdose) became unsteady and fell. CPK was 342 on admission and his urine drug screen was positive for tetrahydrocannabinol. The 24 mg overdose was associated with nausea, sedation and headache. All 3 subjects recovered from their AEs associated with overdose.

Additional subjects were found by the sponsor to have "overdoses" (in excess of assigned dose level) ranging from 6 mg to as high as 60 mg. The observations of these subjects, as described in section 6.5 of the SCS did not yield any new and remarkable clinical information.

7.1.17 Postmarketing Experience

Paliperidone is not marketed in any country (as previously described in this review). Therefore, there is no postmarketing information on the drug. However, risperidone is marketed and is metabolized to the active compound of Pal (9-OH risperidone) as previously described. The submission contains some postmarketing information on risperidone. Postmarketing information of US marketed drugs is provided in periodic safety reports and other submission under the Risperdol® NDA. Postmarketing information on risperidone is also described in current approved Risperdol® labeling.

The Clinical Overview Module 2.5 of the submission summarizes the postmarketing information on risperidone based on the sponsor's results of their pharmacovigilance database (through 4/30/05, in which risperidone was first licensed as an antipsychotic agent in 1992 in the UK). The sponsor indicates that the frequency of case reports of "pituitary tumor, enlargement or related abnormalities for risperidone" is rare (<0.01%) and that their data do not provide evidence for an increased risk for breast cancer in males and females treated with the drug. Worldwide exposure of risperidone is also reported to be over 22 million person-years.

Reviewer Comment. *In the opinion of the undersigned reviewer, postmarketing data poses major limitations in finding a potential safety signal, such that failure to show a safety signal is not adequately assuring that a potential safety signal does not exist.*

Refer to Section 9 of this review for recommendations relevant to a potential carcinogenicity of Pal.

7.1.18 Review of the Literature

Methods of the Sponsor's Literature Search. The sponsor conducted a search of the literature using several standard databases (e.g. Medline, Embase and others) using search terms of 9-hydroxyrisperidone, 9-OH-resperidone, 9-hydroxy-risperidone, paliperidone, and CAS Registry Number 144598-75.4.

237 publications were retrieved from the search. 88 of these articles were selected for review of the full text on the basis of these selected articles containing reference to "safety, tolerability, toxicity, adverse event(s), overdose, pregnancy, lactation, or QT prolongation" found in the title or in the abstract of the given article. However, if the term "toxic" appeared in a given title or abstract, and was used in the context of plasma levels in absence of clinical toxicity or safety information (e.g. articles focusing on methods for monitoring plasma levels), then article was not reviewed by the sponsor.

The results of the sponsor's search are outlined below, as part of the reviewer's comments.

Reviewer Comments on the Results of the Sponsor's Review of the Literature. *The sponsor's review of the literature generally did not review any new or remarkable clinical information. The following are some key findings described in the review:*

- *Potential risperidone-drug interactions are suggested.*
- *Additional articles on pharmacokinetic properties of risperidone*
- *A few articles on QT prolongation in which the following findings are noted by the undersigned reviewer:*
  - *One article (Admamantidis, MM, et al., 2000) is reported to show that Ris is similar to a class III anti-arrhythmic drug with respect to potential arrhtymogenic properties depending on "predisposing factors" based on drug effects on the action potentials recorded from rabbit purkinje fibers (1 uM Ris and 3 uM 9-OH-Ris resulted in a +99±14% and +118±28% change in "class III effects," respectively, in which a "drastic" lengthening in the duration of the action potential and an early-after-depolarization were observed).*
  - *Preclinical evidence for greater binding of 9-OH Ris in myocardium compared to plasma (Titier et cal., 2002).*
- *Extrapyramidal side effects (EPS): EPS rated on the SAAS was found to be correlated to plasma levels of 9-OH Ris and Ris, respectively (Spearman's ρ=0.76, $p<0.01$ between active antipsychotic fraction and SAS score (Yoshimura, et cal, 2001).*
- *Prolactin serum levels were weakly correlated with serums levels of 9-OH Ris (Spearman's ρ=0.28, p value could not be found in the review) and were not correlated with Ris (Bruggeman, et al., 2003).*
- *A few overdose cases involving Ris are reported in the literature but generally did not reveal any new, clinically remarkable findings. However, it is notable that one case of a 21 year old schizophrenia female patient who ingested 50 tablets of 2 mg Ris had sinus tachycardia of 149 bpm and QTc of 414 mscec (type of correction could not be found in the review) at 4 hours post drug intake. 9-OH Ris serum levels were 100 ng/ml and at 48 hours post-ingestion serum levels decreased to 59 ng/ml. Generally, QT or QTc*

intervals of less than 450 msec are not considered clinically remarkable. However, a QT prolongation effect of Ris must be considered which may have greater clinical relevance in patients at risk. Although, note that this patient was female, of which females are generally considered show a longer QT interval than males and may be at greater risk for QT prolongation or adverse effects of QT prolongation.

It is not clear if above key findings are reproduceable. However, the above findings are generally not unexpected given the existing knowledge of drugs in this drug class. Regarding potential drug-drug interactions in the literature, OCPB input on Pal-drug interactions is pending.

7.2 Adequacy of Patient Exposure and Safety Assessments

See previous subsections regarding limitations with the safety data provided. Refer to the final section of this review for comments and recommendations.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Description of Studies, Safety Datasets and other Aspects of Exposure and Safety Assessments. To avoid redundancy, refer to Section 4 for a description of studies and overall enumeration of subjects and refer to Subsection 7.2.1.3 provides the enumeration of subjects by duration of a given treatment. Section 7.1 describes each safety dataset (pooled and unpooled datasets) and the safety assessments conducted.

Patient Exposure. This subsection provides more detailed information in the enumeration of subjects that was not provided elsewhere in this review and within accordance with the Clinical Review MAPP. Enumeration of subjects by treatment group or condition of a given safety dataset is provided as well as enumeration of subjects by additional subcategories (e.g. subcategorized by disposition, number of completers).

Tables in this section were copied from the submission.

Pooled Pivotal Phase III Trials (-303, -304, and -305). The table below is of the 3 pivotal Phase III trials that were pooled for safety analyses.

Enumeration of Safety Populations and Completers in Completed Phase III trials.

Table 3: Number of Subjects Randomly Assigned to Each Treatment Group
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: All Randomized Subjects)

		ER OROS PAL						Olanzapine
	Placebo (N=360) n (%)	3 mg (N=127) n (%)	6 mg (N=235) n (%)	9 mg (N=247) n (%)	12 mg (N=242) n (%)	15 mg (N=115) n (%)	Total (N=966) n (%)	10 mg (N=366) n (%)
All randomized subjects	360 (100)	127 (100)	235 (100)	247 (100)	242 (100)	115 (100)	966 (100)	366 (100)
Subjects evaluable for safety[a]	355 (99)	127 (100)	235 (100)	246 (>99)	242 (100)	113 (98)	963 (>99)	364 (99)

[a] Subjects who received at least 1 dose of study medication.

The following enumerates subjects in various treatment by disposition categories.

Table 4: Study Completion/ Withdrawal Information
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
	Placebo (N=355) n (%)	3 mg (N=127) n (%)	6 mg (N=235) n (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)	15 mg (N=113) n (%)	Total (N=963) n (%)	10 mg (N=364) n (%)
Completed	142 (40)	70 (55)	131 (56)	164 (67)	155 (64)	82 (73)	602 (63)	228 (63)
Withdrawn	213 (60)	57 (45)	104 (44)	82 (33)	87 (36)	31 (27)	361 (37)	136 (37)
Subject choice (subject withdrew consent)	36 (10)	17 (13)	28 (12)	28 (11)	29 (12)	6 (5)	108 (11)	33 (9)
Lost to follow-up	6 (2)	1 (1)	9 (4)	2 (1)	10 (4)	2 (2)	24 (2)	11 (3)
Adverse event	18 (5)	3 (2)	16 (7)	10 (4)	14 (6)	4 (4)	47 (5)	21 (6)
Death	0	0	0	0	0	0	0	1 (<1)
Study medication non-compliance	3 (1)	1 (1)	0	0	3 (1)	2 (>2)	6 (1)	4 (1)
Lack of efficacy	144 (41)	31 (24)	46 (20)	42 (17)	29 (12)	14 (12)	162 (17)	59 (16)
Other	6 (2)	4 (3)	5 (2)	0	2 (1)	3 (3)	14 (1)	7 (2)

1 Elderly (unpooled) Phase III Trial, -302. The following enumerates subjects in various treatment by disposition categories.

Table 5: Study Completion/ Withdrawal Information
(Study R076477-SCH-302 Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)	Total (N=114) n (%)
Completed	26 (68)	64 (84)	90 (79)
Withdrawn	12 (32)	12 (16)	24 (21)
Lack of efficacy	6 (16)	3 (4)	9 (8)
Adverse event	3 (8)	5 (7)	8 (7)
Subject choice (subject withdrew consent)	1 (3)	2 (3)	3 (3)
Death	1 (3)	0	1 (1)
Study medication non-compliance	0	1 (1)	1 (1)
Other[a]	1 (3)	1 (1)	2 (2)

[a] These included discontinuation on Day 36 due to personal circumstances for the subject in the paliperidone group and discontinuation on Day 32 due to lack of study medication at the site for the subject in the placebo group.
Cross-reference: Mod5.3.5.1\R076477-SCH-302\Sec4.1

The following discussion is the enumeration of subjects receiving 6 mg or higher daily doses of Paliperidone in Phase III trials. The dose-level of at least 6 mg was chosen for this discussion since this is the recommended dose for treatment in proposed labeling. Although, note that proposed labeling also suggests a 3 mg daily dose level, as well as higher than 6 mg dose-levels as being effective.

The following outlines the number of ITT Safety subjects and completers in completed Phase III trials of subjects receiving at least 6 mg daily of Paliperidone, as specified:

- *In the 3 pivotal Phase III trials (Studies -303, -304, and -305):*
  - *806 subjects received at least one dose of 6-15 mg of Paliperidone (the Intent-to-treat Safety Population) and an additional 127 subjects were in the ITT safety population of the 3 mg Paliperidone groups*
  - *532 subjects in the 6 to 15 mg Paliperidone group completed the study and 70 subjects in the 3 mg groups completed the study.*

In the elderly phase III 3-12 mg flexible daily dose trial (-302):

- *76 elderly patients received at least one 3-12 mg daily dose of Paliperidone.*
- *64 subjects were completers.*

Ongoing Phase III "Prevention of Recurrence" Trial -301. This ongoing trial has a DB phase and assignment to study drug remains blinded. As of the 5/31/05 cut-off date 462 subjects enrolled in this study. Since this study remains blinded and is ongoing, only information on SAEs and deaths are provided (e.g. enumeration of subjects by treatment, duration of treatment, and other exposure information cannot be found or are not provided, and the sponsor clearly states that safety results on AEs and clinical parameters are not included in the submission).

Enumeration of Subjects in Longer Term Open-label Extension Trials.

Long term exposure was only examined in the above tabulated open-label (OL) extension trials (-702, -703, -704, -705).

Table 6: Study Completion/ Withdrawal Information Through 31 May 2005
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705 Safety Analysis Set)

	---- Pla/Pali ----		---- Pali/Pali ----		---- Olan/Pali ----		- Total Paliperidone -	
	Pali Duration, n (%)		Pali Duration, n (%)		Pali Duration, n (%)		Pali Duration, n (%)	
	≤3 months (N=107)	>3 months (N=128)	≤3 months (N=178)	>3 months (N=505)	≤3 months (N=106)	>3 months (N=143)	≤3 months (N=391)	>3 months (N=776)
Completed	0	5 (4)	0	9 (2)	0	0	0	14 (2)
Ongoing *	46 (43)	97 (76)	83 (47)	364 (72)	31 (29)	107 (75)	160 (41)	568 (73)
Withdrawn	61 (57)	26 (20)	95 (53)	132 (26)	75 (71)	36 (25)	231 (59)	194 (25)
Subject choice(subject withdrew consent)	23 (21)	11 (9)	34 (19)	62 (12)	27 (25)	14 (10)	84 (21)	87 (11)
Lost to follow-up	7 (7)	7 (5)	15 (8)	15 (3)	9 (8)	1 (1)	31 (8)	23 (3)
Adverse event	7 (7)	3 (2)	15 (8)	19 (4)	19 (18)	4 (3)	41 (10)	26 (3)
Death	0	0	0	0	0	1 (1)	0	1 (<1)
Other	24 (22)	5 (4)	31 (17)	36 (7)	20 (19)	16 (11)	75 (19)	57 (7)

* As of 31 May 2005.

So far (as of the May 31, 2005 cut-off date), only 14 subjects have completed the OL extension trials.

The Safety Update Report (SUR) provides additional safety information from the OL extension trial dataset from the following subjects that are enumerated in the table below on the basis of exposure (as copied from the SUR). Note that the number of subjects receiving Pal treatment for at least 6 months and for at least 12 months, respectively, meets ICH guidelines.

Table 12: Total Duration of Paliperidone Exposure – Double-Blind + Open-Label – Through 1 November 2005
(Studies R076477-SCH-702, 703, 704, and 705: Safety Analysis Set)

	-- Pla/Pali -- (N=236)	-- Pali/Pali -- (N=685)	-- Olan/Pali -- (N=249)	---- Total ---- (N=1170)
Total duration of study medication (day)				
N	236	685	249	1170
Category, n (%)				
Week 1-4	35 (15)	4 (1)	44 (18)	83 (7)
Week 5-8	17 (7)	41 (6)	18 (7)	76 (6)
Week 9-12	17 (7)	58 (8)	16 (6)	91 (8)
Week 13-16	5 (2)	48 (7)	13 (5)	66 (6)
Week 17-20	5 (2)	36 (5)	6 (2)	47 (4)
Week 21-24	20 (8)	22 (3)	11 (4)	53 (5)
Week 25-28	30 (13)	14 (2)	23 (9)	67 (6)
Week 29-32	13 (6)	99 (14)	13 (5)	125 (11)
Week 33-36	7 (3)	45 (7)	9 (4)	61 (5)
Week 37-40	4 (2)	31 (5)	7 (3)	42 (4)
Week 41-44	19 (8)	23 (3)	24 (10)	66 (6)
Week 45-48	9 (4)	27 (4)	15 (6)	51 (4)
Week 49-52	36 (15)	44 (6)	34 (14)	114 (10)
> week 52	19 (8)	193 (28)	16 (6)	228 (19)
Mean (SD)	195.4 (126.82)	247.0 (126.33)	188.8 (131.15)	224.2 (130.23)
Median	183.0	237.0	189.0	218.0
Range	(1;391)	(26;453)	(2;379)	(1;453)

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Enumeration of Subjects in Phase I/II Trials.

The 17 Pooled Phase I/II trials of healthy subjects (includes some cross-over studies and some placebo controlled trials) enumerates subjects in this safety dateset.

- Paliperidone, OROS®: 275 subjects
- Immediate release (IR) or other formulations of paliperidone: 219 subjects
- Placebo: 62 subjects

- Risperidone: 52 subjects

The 3 schizophrenia Phase I trials were pooled for integrated safety analyses with subjects receiving at least one dose of study drug enumerated as follows:

- Paliperidone, OROS®: 111 subjects
- IR formulations of paliperidone: 34 subjects
- Risperidone: 55 subjects

Other Phase I/IIa studies are shown in a separate set of tables below that were not pooled for integrated safety analyses since these studies differed drastically in study design such as in the patient population examined (e.g. renal impaired patients) or in were a study focusing on a specific and unique objective (e.g. a study focusing on cardiovascular effects). These 7 studies consisted of a total of 298 subjects received IR or OROS paliperidone of which 93 of these subjects had schizophrenia or schizoaffective disorder.

Section 7.2.1.3 below provides exposure to study drug in various studies.

7.2.1.1 Study type and design/patient enumeration

See section 4 of overall study design of each study and enumeration of subjects.

7.2.1.2 Demographics

Demographic information was previously described in Section 6.1.4 for the completed Phase III trials. Phase I studies were generally conducted on healthy adults, unless otherwise specified in summary tables in Section 4 of this review.

7.2.1.3 Extent of exposure (dose/duration)

Although this subsection only focuses on treatment by dose-level and by duration, in accordance with the MAPP. Other aspects of the extent of exposure were previously provided.

Pooled Completed Pivotal Phase III Trials The following table summarizes exposure by duration of treatment in the pooled, pivotal Phase III trials (of primarily non-elderly adults) which used a parallel-group, fixed-dose design (copied from the submission).

Table 8: Extent of Exposure
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)	15 mg (N=113)	Total (N=963)	10 mg (N=364)
Total duration, days								
N	355	127	235	246	242	113	963	364
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ 7	33 (9)	10 (8)	23 (10)	19 (8)	26 (11)	6 (5)	84 (9)	26 (7)
8 - 14	34 (10)	8 (6)	22 (9)	13 (5)	12 (5)	2 (2)	57 (6)	14 (4)
15 - 21	71 (20)	19 (15)	22 (9)	18 (7)	16 (7)	10 (9)	85 (9)	41 (11)
22 - 28	45 (13)	10 (8)	21 (9)	16 (7)	18 (7)	5 (4)	70 (7)	31 (9)
29 - 35	22 (6)	6 (5)	11 (5)	13 (5)	8 (3)	4 (4)	42 (4)	19 (5)
≥ 36	150 (42)	74 (58)	136 (58)	167 (68)	162 (67)	86 (76)	625 (65)	233 (64)
Mean (SD)	28.4 (13.66)	32.1 (13.44)	31.3 (14.17)	34.5 (12.87)	33.3 (13.95)	36.3 (11.50)	33.3 (13.47)	33.7 (12.73)
Median	28.0	41.0	41.0	42.0	42.0	42.0	42.0	42.0
Range	(1;50)	(1;48)	(1;48)	(1;49)	(1;51)	(1;47)	(1;51)	(1;52)

Note: The duration of exposure includes days on which subjects did not actually take study medication.

Completed Elderly Phase III Trial (Study -302). The following table summarizes exposure (in duration) and the overall mean and median dose-level in subjects in the elderly flexible dose (3-12 mg/day) Phase III trial (copied from the submission):

Table 9: Extent of Exposure
(Study R076477-SCH-302 Safety Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)
Total duration, days		
N	38	76
Category, n (%)		
≤ 7	3 (8)	4 (5)
8 - 14	3 (8)	1 (1)
15 - 21	1 (3)	1 (1)
22 - 28	3 (8)	1 (1)
29 - 35	2 (5)	3 (4)
≥ 36	27 (71)	66 (87)
Mean (SD)	34.9 (12.85)	38.8 (9.37)
Median	42.0	42.0
Range	(3;45)	(4;45)

Note: The duration of exposure includes days on which subjects did not actually take study medication.
Cross-reference: SCH-302/Sec4.6

Ongoing Phase III Prevention Relapse Trial -301
This study has a DB phase and is ongoing with data blinded such that information by treatment group and duration is not provided at this time.

Ongoing Open Label Studies. These studies are ongoing 6 month (in the elderly study, -702) or 52 week OL Pal trials (primarily non-elderly Phase III trials, -703, -704 and -705).

These trials are the sponsor's main source for providing longterm safety, yet trials remain ongoing. See subsection 7.2.3 for a discussion relevant for adequacy of overall exposure and for longterm exposure, while the data supporting conclusions under subsection 7.2.3 are provided below, as required by the Clinical Review MAPP.

The sponsor provides safety data of ITT safety population using a May 31, 2005 cut-off except for deaths and serious adverse events in which an August 31, 2005 cut-off date was employed (in the N000 submission). Updated information was reviewed in a 120-Day SUR which covers exposure (section 7.2.9).

The following table shows exposure duration, mean and median dose for OL trials of which trial employed a flexible dose design of 3 to 12 mg daily of OL Paliperidone using starting daily dose of 6 mg (table is copied from the N000 submission). See section 7.2.9 for updated information.

Table 10: Extent of Exposure to Open-Label ER OROS Paliperidone Through 31 May 2005 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705 Safety Analysis Set)

	Pla/Pali (N=235) n (%)	Pali/Pali (N=683) n (%)	Olan/Pali (N=249) n (%)
Total duration, days			
N	235	683	249
Category, n (%)			
Week 1-4	40 (17)	123 (18)	54 (22)
Week 5-8	40 (17)	87 (13)	30 (12)
Week 9-12	27 (11)	71 (10)	22 (9)
Week 13-16	8 (3)	45 (7)	19 (8)
Week 17-20	13 (6)	39 (6)	23 (9)
Week 21-24	26 (11)	68 (10)	20 (8)
Week 25-28	21 (9)	66 (10)	24 (10)
Week 29-32	14 (6)	51 (7)	18 (7)
Week 33-36	16 (7)	39 (6)	8 (3)
Week 37-40	13 (6)	47 (7)	13 (5)
Week 41-44	13 (6)	26 (4)	13 (5)
Week 45-48	1 (<1)	8 (1)	2 (1)
Week 49-52	1 (<1)	9 (1)	2 (1)
> Week 52	2 (1)	4 (1)	1 (<1)
Mean (SD)	127.8 (94.30)	131.8 (94.29)	121.8 (93.25)
Median	124.0	133.0	112.0
Range	(1;366)	(1;371)	(2;376)

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Table 12: Total Duration of Paliperidone Exposure – Double-Blind + Open-Label – Through 31 May 2005 (Studies R076477-SCH-702, -703, -704, and -705: Safety Analysis Set)

	Pla/Pali (N=235)	Pali/Pali (N=683)	Olan/Pali (N=249)	Total (N=1167)
Total duration of ER OROS paliperidone (day)				
N	235	683	249	1167
Category, n (%)				
Week 1-4	40 (17)	4 (1)	54 (22)	98 (8)
Week 5-8	40 (17)	53 (8)	30 (12)	123 (11)
Week 9-12	27 (11)	121 (18)	22 (9)	170 (15)
Week 13-16	8 (3)	82 (12)	19 (8)	109 (9)
Week 17-20	13 (6)	49 (7)	23 (9)	85 (7)
Week 21-24	26 (11)	30 (4)	20 (8)	76 (7)
Week 25-28	21 (9)	58 (8)	24 (10)	103 (9)
Week 29-32	14 (6)	72 (11)	18 (7)	104 (9)
Week 33-36	16 (7)	59 (9)	8 (3)	83 (7)
Week 37-40	13 (6)	49 (7)	13 (5)	75 (6)
Week 41-44	13 (6)	36 (5)	13 (5)	62 (5)
Week 45-48	1 (<1)	37 (5)	2 (1)	40 (3)
Week 49-52	1 (<1)	16 (2)	2 (1)	19 (2)
> week 52	2 (1)	17 (2)	1 (<1)	20 (2)
Mean (SD)	127.8 (94.30)	171.5 (95.45)	121.8 (93.25)	152.1 (97.46)
Median	124.0	171.0	112.0	140.0
Range	(1;366)	(26;414)	(2;376)	(1;414)

The following table provides mean, median and range of dose-levels of OL trials, combined (as copied from the submission).

Table 11: Paliperidone Exposure - (Mean, Mode, Minimum, and Maximum)
(Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705: Safety Analysis Set)

	Pla/Pali (N=235)	Pali/Pali (N=683)	Olan/Pali (N=249)	Total (N=1167)
Mean dose (days on drug only)				
N	235	681	247	1163
Mean (SD)	9.9 (2.27)	9.8 (2.43)	9.7 (2.13)	9.8 (2.34)
Median	9.3	9.0	9.0	9.0
Range	(3;15)	(3;27)	(3;15)	(3;27)
Mode dose (days on drug only)				
N	233	679	247	1159
Mean (SD)	10.0 (2.59)	9.9 (2.78)	9.7 (2.49)	9.9 (2.68)
Median	9.0	9.0	9.0	9.0
Range	(3;15)	(3;27)	(3;15)	(3;27)
Minimum dose (days on drug only)				
N	235	681	247	1163
Mean (SD)	8.2 (1.99)	8.2 (2.10)	8.2 (1.90)	8.2 (2.04)
Median	9.0	9.0	9.0	9.0
Range	(3;15)	(3;27)	(3;15)	(3;27)
Maximum dose (days on drug only)				
N	235	681	247	1163
Mean (SD)	11.0 (2.76)	11.1 (3.27)	11.2 (3.18)	11.1 (3.15)
Median	12.0	9.0	9.0	12.0
Range	(3;27)	(6;36)	(6;30)	(3;36)

Only exposure during the open label phase is included.

Longterm Exposure When Combining Exposure of DB Lead-in Trials with Exposure of OL Extension Trials.

The following table enumerates total Paliperidone subjects in the safety data set by duration of Paliperidone exposure when combining the 6-week exposure during the DB phase lead-in Studies -302, -303, -304 and -305 with exposure during the OL extension studies (the 26-week Study -702 and the 52-week Studies -703, -704, -705). Also mean and median dose-levels are provided in the table that follows (as provided by the sponsor).

Table 13: Total Duration of Paliperidone Exposure - Double-Blind + Open-Label – Through 31 May 2005
(Studies R076477-SCH-302, -303, -304, -305, -702, -703, -704, and -705: Safety Analysis Set)

	Total Paliperidone (N=1523)
Total duration of study medication (day)	
N	1523
Category, n (%)	
Week 1-4	322 (21)
Week 5-8	255 (17)
Week 9-12	170 (11)
Week 13-16	109 (7)
Week 17-20	85 (6)
Week 21-24	76 (5)
Week 25-28	103 (7)
Week 29-32	104 (7)
Week 33-36	83 (5)
Week 37-40	75 (5)
Week 41-44	62 (4)
Week 45-48	40 (3)
Week 49-52	19 (1)
> Week 52	20 (1)
Mean (SD)	121.7 (101.79)
Median	89.0
Range	(1;414)

Table 14: Mean, Mode, Minimum, and Maximum ER OROS Paliperidone Doses - Double-Blind + Open-Label
(Studies R076477-SCH-302, -303, -304, -305, -702, -703, SCH-704, and SCH-705: Safety Analysis Set)

	Total Paliperidone (N=1523)
Mean dose (days on drug only)	
N	1521
Mean (SD)	9.4 (2.63)
Median	9.0
Range	(3;17)
Mode dose (days on drug only)	
N	1509
Mean (SD)	9.4 (3.13)
Median	9.0
Range	(3;27)
Minimum dose (days on drug only)	
N	1521
Mean (SD)	7.7 (2.55)
Median	9.0
Range	(0;15)
Maximum dose (days on drug only)	
N	1521
Mean (SD)	11.0 (3.80)
Median	12.0
Range	(3;60)

See a discussion and reviewer comments on longterm exposure relevant to ICH guidelines in section 7.2.3, in accordance with the Clinical Review MAPP.

Phase I/II Trials.
A total of 152 subjects in the above healthy subject Phase I/II trials received at least one dose of 3 to 6 mg of Paliperidone and 200 subjects received at least one dose of a higher dose level of 9 to 15 mg. Most subjects completed these trials (generally over 90% of subjects in any given group among the trials).

Refer to section 4 of the number of subjects in each set of pooled Phase I and individual Phase I/II trials.

Refer to Section 7.2.9 for updated longterm exposure and safety information that met ICH guidelines for longterm exposure.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

In accordance with the Clinical Review MAPP this subsection describes secondary datasources.

The 120-Day SUR provided the bulk of longterm exposure data, although up to approximately 6 months of longterm exposure results were provided in the N000, as previous discussed.

See Section 4 for a listing of additional submissions and the review strategy.

Refer to section 7.2.3 regarding a more detailed discussed on longterm exposure relevant to ICH guidelines (in accordance with the MAPP).

A review of the literature is provided in this review. Pal has not been marketed in any country such that postmarketing data does not exist. The sponsor provided some postmarketing information on Risperdol,® as described in section 7.1.17 of this review. Current approved labeling of Risperdol® provides postmarketing information and other safety information on this related drug.

To avoid redundancy and to enhance continuity and flow in this review results of other sections describing safety results from the above secondary data sources are not described in this section.

The last section of this review provides recommendations relevant to safety.

7.2.2.1 Other studies

Other studies are addressed in other sections of this review (refer to Section 7.1 and Section 4 of this review and section 7.1.12).

7.2.2.2 Postmarketing experience

Paliperidone is not approved for the market in any country, as previously described, in subsection 7.1.17 which also discusses postmarketing information on the approved related drug, risperidone (Risperdol®).

7.2.2.3 Literature

Refer to Section 7.1.18 which includes a description of methodology and findings found in the submission, as previous described.

7.2.3 Adequacy of Overall Clinical Experience

In accordance with the Clinical Review MAPP, this section discusses adequacy in meeting ICH guidelines on the extent and duration of exposure for assessing safety.

Reviewer Comment.
The information provided in the 120-Day SUR met ICH guidelines for 6 and 12 month exposure and ICH guidelines were met for short-term exposure within an adequate dose-range (as provided in the N000 submission).

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This topic is regarding preclinical information. Refer to Section 3 of this review for any relevant and significant preclinical findings identified and conveyed to the undersigned reviewer by the Pharmacology Toxicology Reviewer who is conducting the preclinical review.

7.2.5 Adequacy of Routine Clinical Testing

Concerns with the clinical data were previously discussed in appropriate sections in this review. Refer to the last section of this review for any additional comments or recommendations that may apply to this topic.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Refer to Section 3 of this review which describes any relevant and significant issues conveyed by the OCPB reviewer conducting the review of studies on this topic that were submitted in this NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

See the final section of this review.

7.2.8 Assessment of Quality and Completeness of Data

Several questions remain at the time of this writing regarding quality and completeness of the safety results. Before discussing questions relevant to this topic, it is important to note that clinical research databases and the ability to capture all adverse events can be a challenge in any given clinical trial (e.g. consider the AE coding system that may be employed, consider the potential diversity across investigators in how a clinical situation may be assessed and diagnosed that may be subject to the clinical practices of their region, their training and other factors). While keeping this in mind, questions remain regarding the quality and completeness in capturing all subjects with a specific type of adverse event in the AE database, such as suicidality (refer to Section 4.1.4.6) and possibly others that occurred during the treatment phase of clinical trials (e.g. such as events believed to be part of an overall pre-existing condition and/or adverse events captured using a broader AE term that could have been reported using a term such as "excacerbation of schizophrenia"). Note the following:

- *The sponsor made an effort to identify subjects with suicidality that were reported using another SAE term that they did not capture in their results on suicidality (they reported these uncaptured subjects in the original N00 submission). This is described in section 7.4.1.6 of this review. The sponsor accomplished this by reviewing safety alert forms. So the following questions remain:*
  - *Could there could be additional uncaptured subjects that were not considered as requiring a safety alert form (so were not reviewed for suicidality)? It would seem that any subject with suicidality would have a Safety Alert form submitted (even it another term were used such as "exacerbation of schizophrenia") since suicidality is potentially life-threatening but it is not clear to the undersigned reviewer if this was the case for all such subjects (e.g. if the investigator considered it to be part of an overall condition).*
  - *Are other subjects that were not captured for a given specific type of AE because they were events considered as part of an overall condition or reported using a broader AE term?*

While it is helpful to use broader AE terms such as "exacerbation of schizophrenia" that could be considered clinically representative of the overall clinical picture at the time of the event(s) (such as a subject who becomes suicidal and increasingly psychotic who is believed to have these events as part of their disorder), it is also important to include more specific AE terms that do not infer causality (e.g. psychosis, suicidal ideations). Without recording these additional terms (as AE terms in the CRF) it would appear that these more specific events would not be captured in the sponsor's AE database. Also if a given set of events were not considered to be of the nature to warrant submitting a safety alert report then it is not clear how multiple events would be recorded in the case that

one term is believed to capture all events (e.g. "dizziness" in a patient that was also having a decrease in blood pressure). Section 7.1.4.6 of this review for more details on capturing and enumerating events of suicidality. Teleconference minutes with the sponsor's clarification on their search methods for revealing uncaptured cases of suicidality are provided later in this subsection (to be entered in DFS as a separate document).

- *In addition to the above, there is also the question of capturing subjects who withdrew from the study early for reasons that may be unclear (e.g. subjects who withdrew consent or were noncompliant that in turn, led to early withdrawal). Early withdraw such as a subject that is noncompliant or a subject who withdraws consent (or possibly who has exacerbation of their psychotic symptoms) could in some cases be associated with clinically remarkable adverse events or an SAE at or near the time that the given subject was noncompliant leading to their early withdrawal. The sponsor was inquired about this concern and was given examples of subjects (see Attachment 1 of this review for a listing of these subjects to which a response is anticipated but appear to be pending at this time). The following is one example of these subjects:*
    - Subject 503018 in Study -305 in the original NDA submission was withdrawn due to noncompliance" after 4 days of stopping the study drug (drug stopped on Day 20 and withdrew "due to noncompliance" on Day 24) who had abnormal LFTs on Day 15 and "onward" (elevations of up to approximately 5 times the ULN, first observed on Day 15). Values normalized on Day 29 (9 days post-treatment cessation). This subject was found in the narrative section of subjects but was not checked off in the narrative summary table (preceding the narratives) as having either an SAE or as "premature discontinued." This subject cannot be found in line listings of SAEs or ADOs. The narrative indicates that the elevations in LFTs were not reported as AEs. Please clarify and provide the rationale for how events of elevated LFTs were actually reported in subjects and clarify why the drug was stopped and why the subject was noncompliant.
    - Subject 100057 also had AEs that he could not tolerate on the same day of having study medication stopped "permanently on Day 22 as the subject withdrew consent." This subject is recorded on the narrative summary table as only having an SAE and is not checked off as being an adverse dropout (the "premature discontinued" column on page 1773). The following are excerpts from the narrative page 1815:

The subject was discharged from the hospital portion of the study on Day 20. At the scheduled Day 22 visit, he reported side-effects that he "could not tolerate" (restlessness and inability to sleep) (source: CIOMS). Study medication was permanently stopped on Day 22 as the subject withdrew consent. Vital signs were within normal limits but slightly higher than at earlier readings (138/91 mmHg standing; 141/72 mmHg supine); temperature was 36.4 degrees. Laboratory analyses on Day 22 (end of study) revealed a creatine kinase (CK) of 2201 U/L (reference range: 18-198 U/L); all other laboratory values were reported within the normal range. At baseline (Day -2), the baseline creatine kinase value was 186 U/L. The serious adverse events "elevated CK" and "neuroleptic malignant syndrome (acute EPS side effects)" were reported on Day 24 and Day 25, respectively; the elevated CK was considered life threatening.

- *Another reason for concern in identifying and enumerating subjects with a specific type of adverse event is that subjects with clinically remarkable adverse events could not be found described in key and relevant in-text sections of the integrated safety summary section of the NDA which was found in the SCS (a few remarkable subjects were described in some key sections of the SCS but often subject numbers were not provided with reference to a narrative location). The following subject is an example (the sponsor was inquired about this subject and others as listed in Attachemtn 1 of this*

review (to which responses are either pending or were received and are under review). This subject was found briefly described in an in-text safety section of one of the study reports (CSRs) of the Phase III trials (on page 122 of the CSR of Study -304). It is also not clear to the undersigned reviewer if "exacerbation of schizophrenia" in this subject which was reported as an AE leading to early withdraw (reported as an adverse dropout) occurred secondarily to the clinically remarkable cardiovascular events (e.g. a given subject may not report symptoms or may not appear to be in physical distress due to an acute psychotic state that may have been exacerbated secondarily to undetected physical distress):

- *Subject 300541 had "syncope," bradycardia and "pauses" described but the terms syncope and pause or sinus pause could not be found in line listings of ADOs or SAEs (although the SAE listing has this subject listed with terms of bradycardia, dizziness, heart rate irregular and hypotension as preferred terms and as verbatim terms except the heart rate irregular had the verbatim term of delay in pulse). The SAE listing also shows that no action was taken with treatment ("none" listed under the "Action Taken with Treatment" column). According to the narrative and the ADO line-listing of this subject, the study drug was stopped due to "exacerbation of schizophrenia" (the ADO line listing indicates that the study was drug stopped on Day 5). The above cardiac related SAEs were reported on Day 5 (hypotension and dizziness) and Day 6 (heart rate irregular and bradycardia). This subject also met outlier criteria for orthostatic hypotension but a description of this subject in in-text sections of the SCS focusing on orthostatic hypotension, potential pro-arrhythmic related events, on SAEs or ADOs, or on subjects who were clinically remarkable outliers on vital signs or ECG assessments could not be found in the SCS (a word search for this subject in the SCS pdf file was conducted by the undersigned using the subject's number and results are shown below).*
- *The following are the results of a search in the SCS for this subject (by the undersigned reviewer) by using the "find" tool in the PDF file of the SCS (using the subject number):*
  - *The subject number was found by the PDF "find" tool in the line listings for ADOs and SAEs, as above which was on pages 1809 and 1861 of the SCS (in appendices).*
  - *The subject number was also found in the narratives on page 2555 (a 2 page narrative) in an appendix of the SCS.*
  - *The subject number was also found in a listing of subjects meeting outlier criteria on page 308 of a 475 page table in an appendix of the SCS on page 4350 (which is page 308 of the 475 page table). In this table a standing and supine HRs of 38 and 40 bpm, respectively which were listed on Day 6 of the study compared to standing and supine heart rates of 80-92 and 90-76 bpm, respectively on previous assessments (includes: 2 baseline assessments and assessments on Days 2, 3, and 4.*
  - *The above subject is described from a clinical perspective in Section 7.1.3.3. C of this review but it is noteworthy that 3 subjects with sinus pauses and syncope are described in olanzapine labeling.*

Section 9 of this review discusses this issue further and a listing of outstanding questions in which responses are yet to be received at the time of this righting are provided in the Attachment 1of this review. Section 4.1 provides a list of responses received so far but that have not been fully reviewed due to their late arrival during the review cycle.

On a final note, limitations found with some of the safety results of some of the clinical parameters were previously described in this review preceding the presentation of the results in each corresponding section (e.g. refer to Section 7.1.7.3.1 on laboratory parameters regarding limitations with urinalysis results, and of results on parameters that were found for only about half the subjects in a given treatment group). However, other data was provided that generally appeared to offset these limitations.

The following summarizes meeting notes to be entered into DFS (Team Leader, Dr. Ni Khin concurred on the minutes below) in which the sponsor provided further clarification on their methods in finding uncpatured subjects in the results on suicidality (after the undersigned reviewer reviewed their N005 response to our question related to this topic):

> In our Tcon today at 1:30 pm with Dr. Michelle Kramer and Heddie, Dr. Kramer explained to us (Drs. Ni Khin, Team Leader and Dr. Karen Brugge, reviewer) that all CIOMS forms (so any and all SAEs) of the Phase III trials were reviewed for any comments of suicidality, aggression or agitation that may have been written on the CIOMS forms by the investigator. If such comments were found in a given CIOMS but were not coded in the CRFs as suicidality-related AEs or SAEs, then the investigator was asked why (by the sponsor). If the investigator did not think it should be coded as a separate AE or SAE, then comments were transferred over to the comment section of the CRFs but were not coded as AEs or SAEs and were therefore not captured in their AE, ADO or SAE database. Therefore, if for example a given patient had suicidality related events (e.g. complained of suicidal thoughts) but the investigator thought it was part of there overall clinical condition or that it was adequately captured by another SAE term (e.g. exacerbation of schizophrenia) then suicidality was not coded and captured in the database as an SAE or AE of suicidality.

The following are examples of subjects identified in a response submission (N005 dated 6/15/06) from the sponsor about suicidality cases in which suicidality was not reported as an AE or SAE term:

- 300381 ER OROS PAL 6 mg (see example below of suicidality comments that the sponsor found upon review of CIOMS forms)
- 300301 ER OROS PAL 12 mg
- And Others

In the original N000 submission on page 1898 in the SCS the following comments on suicidality were found by the sponsor in the CIOMS forms for each of these subjects (as copied from the submission):

```
R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 1 NEW RECORD OUTSIDE
FIELD: 13. OTHER - ABNORMAL - NICOTINE WITHDRAWAL
R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 2 PT. REFUSED VITAL SIGNS
R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 3 PT. REFUSED TO
PARTICIPATE AND COMPLY WITH POST-STUDY VISIT.
```

R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 4 PER SAE REPORT, SUBJECT PRESENTED TO ER ON [redacted] WITH SUICIDAL IDEATION. PER CLINICAL ASSESSMENT THIS IS A SUICIDAL IDEATION. PER [redacted] , THE INVESTIGATOR DOES NOT WANT TO ADD SUICIDAL IDEATION
R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 5 INVESTIGATOR EXPLAINS: SUBJECT [redacted] HAD TWO HOPITALISATIONS ONE BEGINNING [redacted] .BOTH ARE CONSIDERED EXACERBATION OF SCHIZOPHRENIA.
R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 6 SUICIDAL IDEATION IS CONSIDERED A PART OF THE CLINICAL SYMPTOMS AND NOT A DIAGNOSIS SEPARATELY.BOTH HOSPITALISATIONS ARE SERIOUS

R076477-SCH-304-0041-300301 ER OROS PAL 12 mg YES YES 1 PER SAE REPORT, SUBJECT WANTED TO COMMIT SUICIDE AND HAS POSSIBLE SUICIDAL IDEATION PER CLINICAL ASSESSMENT. PER [redacted] THE INVESTIGATOR DOES NOT WANT TO ADD SUICIDAL IDEATION TO CRF.
R076477-SCH-304-0041-300301 ER OROS PAL 12 mg YES YES 2 INVESTIGATOR EXPLAINS: THE PATIENT DID REPORT SUICIDAL IDEATION WITHOUT A PLAN TO A POLICE OFFICER PRIOR TO HOSPITALISATION ADMISSION [redacted] AFTER HE HAD BEEN ASSAULTED.

7.2.9 Additional Submissions, Including Safety Update

7.2.9.1 120-Day Safety Update Report

The 4 month Safety Update Report was submitted. Italicized text is used for sections that contain reviewer comments.

The bulk of safety data in the SUR comes from the OL extension trial safety dataset which includes ongoing trials (Studies -702 through -705 combined). This dataset now meets ICH guidelines for exposure of at least 12 months, whereas this dataset only met ICH guidelines for 6 month exposure in the original submission. Therefore, the focus of the review of the SUR is on results from this longterm safety dataset. The table below was provided by the sponsor and shows the results on Pal exposure in this dataset.

Table 12: Total Duration of Paliperidone Exposure – Double-Blind + Open-Label – Through 1 November 2005
(Studies R076477-SCH-702, 703, 704, and 705: Safety Analysis Set)

	— Pla/Pali — (N=236)	— Pali/Pali — (N=685)	— Olza/Pali — (N=249)	— Total — (N=1170)
Total duration of study medication (day)				
N	236	685	249	1170
Category, n (%)				
Week 1-4	35 (15)	4 (1)	44 (18)	83 (7)
Week 5-8	17 (7)	41 (6)	18 (7)	76 (6)
Week 9-12	17 (7)	58 (8)	16 (6)	91 (8)
Week 13-16	5 (2)	48 (7)	13 (5)	66 (6)
Week 17-20	5 (2)	36 (5)	6 (2)	47 (4)
Week 21-24	20 (8)	23 (3)	11 (4)	53 (5)
Week 25-28	30 (13)	14 (2)	23 (9)	67 (6)
Week 29-32	13 (6)	99 (14)	13 (5)	125 (11)
Week 33-36	7 (3)	45 (7)	9 (4)	61 (5)
Week 37-40	4 (2)	31 (5)	7 (3)	42 (4)
Week 41-44	19 (8)	23 (3)	24 (10)	66 (6)
Week 45-48	9 (4)	27 (4)	15 (6)	51 (4)
Week 49-52	36 (15)	44 (6)	34 (14)	114 (10)
> week 52	19 (8)	193 (28)	16 (6)	228 (19)
Mean (SD)	195.4 (126.82)	247.0 (126.33)	188.8 (131.15)	224.2 (130.23)
Median	183.0	237.0	169.0	218.0
Range	(1;391)	(26;453)	(2;379)	(1;453)

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The remainder of the safety data in the SUR is from unpooled studies that include the following:

- *Sudy -301: the "preventions of recurrence" trial that was ongoing at the time of the N000 submission but is now completed,*
- *Study -701: the OL extension study of which Study -301 was the lead-in study.*

The focus of the review of the SUR was on safety data from the pooled longterm OL extension trial dataset (-702 through -705, combined) for the portions of safety data that are described in this review.

Only SAEs and ADOs from the unpooled studies were reviewed, since these 2 trials (studies -301 and -701) provide limited longterm safety data, in contrast to the information provided by the OL extension-trial longterm-safety dataset.

The following paragraphs discuss the rationale for the above-described review strategy.

The longterm OL extension trial dataset (-702 through -705, combined) is an integrated safety dataset that has a substantially larger sample size of subjects receiving at least 6 months and at least 12 months of Pal treatment, respectively than the unpooled Studies -301 and -701. In the integrated OL trial dataset a total of 1170 subjects received OL treatment of which 228 subjects received over 52 weeks of Pal treatment (this enumeration includes Pal treatment in subjects assigned to DB Pal in the lead-in short-term Phase III trials). The remainder of safety data in the SUR came from unpooled trials (-301 and -701) with smaller sample sizes of subjects exposed to shorter duration of treatment. Only approximately 241 subjects received only 14 weeks of treatment in Study -301and only a few subjects received over 16 weeks of OL Pal

treatment in the OL extension trial to Study -301 (e.g. 9 subjects so far have received 17-20 weeks of treatment and only 6 subjects have received 49-52 weeks of treatment, based on Table 8 on page 57 of the SUR). Therefore, the combined dataset of Studies -702 through -705 is the focus of this review and for the purpose of examining safety results with longterm treatment.

Short-term DB placebo controlled Phase III data was also limited in the SUR, since only one study, Study -301 had a placebo controlled, DB phase. The N000 provided sufficient safety information on short-term safety that came from an integrated short-term Phase III dataset of pivotal trials (Studies -303, -304 and -305, combined). The sample size of randomized DB Pal subjects in Study -301 is only approximately 100 subjects of which only approximately 20 subjects exceeded 12 weeks of DB treatment. This sample size is contrasted to the substantially larger sample size of subjects in the pivotal Phase III trials (Studies -303, -304 and -305, combined) that are already provided in the original NDA and previously described in this review. Therefore, only SAEs and ADOs in from the unpooled studies -701 and -301 that were provided in the SUR were reviewed.

Reviewer Comments/Caveats on the Above Results
The integrated longterm (OL extension trial) dataset was presented in the N000 submission with treatment groups subdivided by duration of OL Pal treatment (≤3 months versus > 3 months for each treatment group categorized by previous DB drug assignment in the lead-in study). In the SUR, this updated dataset is presented with the treatment subgroups categorized by duration of exposure as follows: ≤ 6months versus > 6 months categories. As previously noted more subjects were exposed to over 6 months of treatment in this updated dataset. The rationale for subdividing groups in this manner is not clear to the undersigned, since it would be more informative to have presented data over time for all subjects combined (but subdivided only by previous DB treatment assignment and not by duration of exposure). Perhaps one reason for the sponsor subdividing subjects by duration of exposure is that the longer exposed subgroup is more likely to represent subjects who tolerate the drug better than at least some of the subjects who had less time of exposure in these ongoing OL trials.

One potential concern about the disposition of the subjects is discussed in the following. Table 4 in the SUR shows that 30% or more of subjects in any given treatment subgroup with 6 months or less exposure (in the OL extension trial dataset) withdrew early for "other" reason (not due to other reasons: withdrew consent, lost to follow-up, due to an AE, or death). It is recommended that the sponsor be inquired about why these subjects withdrew early since it represents a large proportion of subjects. Despite this large dropout of subjects, the sample size of subjects remaining in the study is sufficient and meets ICH guidelines, as previously discussed.

Deaths
The following table is a comprehensive listing of all deaths of all Phase I-III trials as of the November 1, 2005 cut-off day. There are no deaths that occurred after the cut-off date through

Phase 3 Open-Label Studies

Treatment Group: Pla/Pali, ≤6 months

100315	70	Bronchopneumonia	157	None	Not related
(R076477-SCH-703)	Male	Bronchopneumonia			

Treatment Group: Pali/Pali, >6 months

100416	31	Completed suicide	238	None	Not related
(R076477-SCH-703)	Female	Fall from 3rd floor			

Treatment Group: Olan/Pali, >6 months

100416	31	Completed suicide	238	None	Not related
(R076477-SCH-703)	Female	suicide with medication[4]			

Note: Gray shading indicates a death that occurred after the cut-off date for NDA 21-999 (31 May 2005) and before the cut-off date for this Update (1 November 2005).

[a] Study day is in reference to the start of double-blind medication, except for Subject 100744 (start of run-in phase).

[b] Relationship based on assessment of investigator.

[c] Subject was withdrawn from the study due to a serious adverse event (electrocardiogram QT corrected interval prolonged) and died of non-treatment-emergent bronchopneumonia 4 days after receiving the last dose of study medication.

[d] Subject ingested venlafaxine and lorazepam.

SAEs.

SAEs and ADOs in Study -301.

Reviewer Comment and Summary: *No new, unexpected ADOs and SAEs were reported that are not already found in the N000 submission, with some possible exceptions. These possible exceptions were incorporated in previous sections of this review that focused on individual subjects with remarkable events, SAEs or ADOs in a previous section (Section 7.1.3.3) of this review.*

ADOs of Potential Hemodynamic or Cardiac Drug Effects. These subjects were incorporated in Section 7.1.3.3 of this review. An additional new ADO (new by nature of the event) was found that was not previously reported that appears to be an isolated event, associated with risk factors in a patient with positive past history for this event. Therefore, it does not appear t be drug-related. The following provides more information on this subject:

> *Venous thrombosis was reported as an SAE in subject 100738 but this subject had a prior event of this nature 1 month prior to this study (phlebitis) and had risk factors (49 year old, obese, woman with chronic hepatitis by history).*

The following table was provided in the SUR.

Table 31: Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term - Run-In and Stabilization Phases (Study R076477-SCH-301: All Treated Analysis Set)

Body System or Organ Class Dictionary-derived Term	ER OROS PAL (RI/ST) (N=530) n (%)
Total no. subjects with serious AE	30 (6)
Psychiatric disorders	25 (5)
Schizophrenia	10 (2)
Psychotic disorder	8 (2)
Agitation	4 (1)
Aggression	2 (<1)
Suicidal ideation	2 (<1)
Depression	1 (<1)
Hallucination	1 (<1)
Intentional self-injury	1 (<1)
Paranoia	1 (<1)
Suicide attempt	1 (<1)
Injury, poisoning and procedural complications	2 (<1)
Injury	1 (<1)
Intentional overdose	1 (<1)
Blood and lymphatic system disorders	1 (<1)
Thrombocytopenia	1 (<1)
Gastrointestinal disorders	1 (<1)
Swollen tongue	1 (<1)
Hepatobiliary disorders	1 (<1)
Cholelithiasis	1 (<1)
Nervous system disorders	1 (<1)
Akathisia	1 (<1)
Dyskinesia	1 (<1)
Tremor	1 (<1)
Social circumstances	1 (<1)
Social problem	1 (<1)

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6 subjects, each with the following respective SAEs were also ADOs (study drug was permanently discontinued): intentional overdose and suicide attempt (1 subject), suicidal ideation, swollen tongue, thrombocytopenia, agitation, and cholelithiasis.

SAEs of schizophrenia and aggression in 1 subject lead to a dose adjustment and dyskinesia and akathisia in another subject lead to a temporary cessation of treatment.

Table 32: Treatment-Emergent Serious Adverse Events by Preferred Term - Double-Blind Phase
(Study R076477-SCH-301: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)	Total (N=206) n (%)
Total no. subjects with serious AE	16 (16)	8 (8)	24 (12)
Psychiatric disorders	15 (15)	6 (6)	21 (10)
Schizophrenia	10 (10)	5 (5)	15 (7)
Psychotic disorder	4 (4)	0	4 (2)
Agitation	0	1 (1)	1 (<1)
Completed suicide*	1 (1)	0	1 (<1)
Suicidal ideation	1 (1)	0	1 (<1)
Injury, poisoning and procedural complications	1 (1)	1 (1)	2 (1)
Gun shot wound*	1 (1)	0	1 (<1)
Treatment noncompliance	0	1 (1)	1 (<1)
Vascular disorders	0	2 (2)	2 (1)
Hypertension	0	1 (1)	1 (<1)
Venous thrombosis	0	1 (1)	1 (<1)
Cardiac disorders	0	1 (1)	1 (<1)
Tachycardia	0	1 (1)	1 (<1)
Musculoskeletal and connective tissue disorders	0	1 (1)	1 (<1)
Musculoskeletal chest pain	0	1 (1)	1 (<1)

* This event resulted in death of subject (see Section 2.1.2).
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Table 33: Serious Adverse Events Through 1 November 2005
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=13) n (%)	Pla/Pali >6 months (N=67) n (%)	Pali/Pali <=6 months (N=2) n (%)	Pali/Pali >6 months (N=70) n (%)	Pali(NO DB)/Pali <=6 months (N=59) n (%)	Pali(NO DB)/Pali >6 months (N=24) n (%)
Total no. subjects with serious adverse events	2 (15)	3 (4)	0	1 (1)	0	0
Psychiatric disorders	1 (8)	2 (3)	0	1 (1)	0	0
Schizophrenia	0	1 (1)	0	1 (1)	0	0
Paranoia	0	1 (1)	0	0	0	0
Suicide attempt	1 (8)	0	0	0	0	0
Injury, poisoning and procedural complications	0	1 (1)	0	0	0	0
Tibia fracture	0	1 (1)	0	0	0	0
Nervous system disorders	1 (8)	0	0	0	0	0
Syncope	1 (8)	0	0	0	0	0

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 33: Serious Adverse Events Through 1 November 2005 (Continued)
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Total Pali <=6 months (N=74) n (%)	Total Pali >6 months (N=161) n (%)
Total no. subjects with serious adverse events	2 (3)	4 (2)
Psychiatric disorders	1 (1)	3 (2)
Schizophrenia	0	2 (1)
Paranoia	0	1 (1)
Suicide attempt	1 (1)	0
Injury, poisoning and procedural complications	0	1 (1)
Tibia fracture	0	1 (1)
Nervous system disorders	1 (1)	0
Syncope	1 (1)	0

See footnotes on the first page of the table.
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Table 34: Serious Adverse Events Through 1 November 2005
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Total no. subjects with serious adverse events	17 (17)	12 (9)	40 (19)	56 (12)	33 (31)	14 (10)	90 (22)	82 (11)
Psychiatric disorders	12 (12)	9 (7)	35 (17)	43 (9)	30 (28)	11 (8)	77 (19)	63 (8)
Psychotic disorder	7 (7)	2 (1)	14 (7)	20 (4)	12 (11)	4 (3)	33 (8)	26 (3)
Schizophrenia	2 (2)	3 (2)	15 (7)	15 (3)	13 (12)	3 (2)	30 (7)	21 (3)
Depression	0	2 (1)	1 (<1)	4 (1)	2 (2)	1 (1)	3 (1)	7 (1)
Agitation	2 (2)	1 (1)	3 (1)	2 (<1)	5 (5)	1 (1)	10 (2)	4 (1)
Hallucination, auditory	0	0	0	4 (1)	0	0	0	4 (1)
Suicidal ideation	2 (2)	1 (1)	3 (1)	3 (1)	0	0	5 (1)	4 (1)
Acute psychosis	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Anxiety	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Completed suicide	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Depressed mood	0	0	0	2 (<1)	0	0	0	2 (<1)
Aggression	2 (2)	1 (1)	0	0	4 (4)	0	6 (1)	1 (<1)
Alcoholism	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Confusional state	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Delusion	0	0	2 (1)	1 (<1)	0	0	2 (<1)	1 (<1)
Paranoia	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Polydipsia psychogenic	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia, paranoid type	0	0	0	1 (<1)	0	0	0	1 (<1)
Self-injurious ideation	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Sleep disorder	0	1 (1)	0	0	0	0	0	1 (<1)
Suicide attempt	1 (1)	1 (1)	2 (1)	0	1 (1)	0	4 (1)	1 (<1)
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
Insomnia	0	0	1 (<1)	0	2 (2)	0	3 (1)	0

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 34: Serious Adverse Events Through 1 November 2005 (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Infections and infestations								
Nasopharyngitis	0	0	0	2 (<1)	0	0	0	2 (<1)
Bronchitis acute	0	0	0	1 (<1)	0	0	0	1 (<1)
Cellulitis	0	0	0	1 (<1)	0	0	0	1 (<1)
Measles	0	0	0	1 (<1)	0	0	0	1 (<1)
Perianal abscess	0	0	0	1 (<1)	0	0	0	1 (<1)
Pulmonary tuberculosis	0	0	0	0	0	1 (1)	0	1 (<1)
Sinusitis	0	0	0	1 (<1)	0	0	0	1 (<1)
Urinary tract infection	0	0	0	1 (<1)	0	0	0	1 (<1)
Hepatitis A	0	0	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	0	0	0	0	1 (1)	0	1 (<1)	0
Nervous system disorders	1 (1)	2 (1)	4 (2)	5 (1)	1 (1)	0	6 (1)	7 (1)
Akathisia	0	0	0	2 (<1)	1 (1)	0	1 (<1)	2 (<1)
Dizziness	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Dystonia	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Ischaemic stroke	0	1 (1)	0	0	0	0	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Transient ischaemic attack	1 (1)	0	0	0	0	0	1 (<1)	0

See footnotes on the first page of the table.

Table 34: Serious Adverse Events Through 1 November 2005 (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
General disorders and administration site conditions	0	0	1 (<1)	4 (1)	1 (1)	0	2 (<1)	4 (1)
Pyrexia	0	0	0	2 (<1)	0	0	0	2 (<1)
Cyst	0	0	0	1 (<1)	0	0	0	1 (<1)
Irritability	0	0	0	1 (<1)	0	0	0	1 (<1)
Chills	0	0	1 (<1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0
Injury, poisoning and procedural complications								
Fall	0	0	0	1 (<1)	0	0	0	1 (<1)
Road traffic accident	0	1 (1)	0	0	0	0	0	1 (<1)
Traumatic haematoma	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Alcohol poisoning	1 (1)	0	0	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Overdose	0	0	0	0	1 (1)	0	1 (<1)	0
Investigations	1 (1)	0	0	2 (<1)	0	0	1 (<1)	2 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Metabolism and nutrition disorders	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Diabetes mellitus	0	0	0	1 (<1)	0	0	0	1 (<1)
Hyponatraemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Hypokalaemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Benign neoplasm of skin	0	0	0	0	0	1 (1)	0	1 (<1)
Colon neoplasm	0	0	0	1 (<1)	0	0	0	1 (<1)

See footnotes on the first page of the table.

Table 34: Serious Adverse Events Through 1 November 2005 (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (<1)	1 (<1)	0	1 (1)	1 (<1)	2 (<1)
Asthma	0	0	0	0	0	1 (1)	0	1 (<1)
Dyspnoea	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Pneumonia aspiration	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood and lymphatic system disorders	0	0	0	1 (<1)	0	0	0	1 (<1)
Anaemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Gastrointestinal disorders	1 (1)	1 (1)	0	0	0	0	1 (<1)	1 (<1)
Crohn's disease	0	1 (1)	0	0	0	0	0	1 (<1)
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Hepatobiliary disorders	0	0	0	1 (<1)	0	0	0	1 (<1)
Cholelithiasis	0	0	0	1 (<1)	0	0	0	1 (<1)
Cardiac disorders	1 (1)	0	2 (1)	0	2 (2)	0	5 (1)	0
Bundle branch block	1 (1)	0	0	0	0	0	1 (<1)	0
Myocardial infarction	0	0	1 (<1)	0	0	0	1 (<1)	0
Sinus tachycardia	0	0	0	0	1 (1)	0	1 (<1)	0
Tachycardia	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Social circumstances	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Drug abuser	0	0	1 (<1)	0	2 (2)	0	3 (1)	0

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120

The following additional SAEs were found on page 121 of SUR (copied from the submission):

"Serious Adverse Events From 2 November 2005 through 31 December 2005
Reports of serious adverse events were received by the sponsor for 9 subjects in the ongoing open-label Phase 3 trials from 2 November 2005 through 31 December 2005. No subjects died. There was 1 suicide attempt (by overdose with acebutolol hydrochloride) and 1 overdose (a subject who took an extra 15 mg dose of ER OROS paliperidone for 8 days due to disturbed sleep; this subject was subsequently hospitalized for suicidal ideation and schizophrenia). The other non-fatal serious adverse events involved hospitalizations for exacerbations of schizophrenia (n=3), psychotic disorder (n=2), and anxiety, agitation, varicocele, suicidal ideation, and delusion (n=1 each). Clinical safety reports (CIOMS forms) for these subjects are provided in Appendix 3.6."

ADOs in Studies -301, -701 and ADOs of the Pooled, OL-trial Dataset

Table 35: Treatment-Emergent Adverse Events Leading to Study Discontinuation by MedDRA Preferred Term - Run-In and Stabilization Phases (Study R076477-SCH-301: All Treated Analysis Set)

Body System or Organ Class Dictionary-derived Term	ER OROS PAL (RI/ST) (N=530) n (%)
Total no. subjects who discontinued due to AE	27 (5)
Psychiatric disorders	10 (2)
Aggression	2 (<1)
Agitation	2 (<1)
Insomnia	2 (<1)
Anxiety	1 (<1)
Depression	1 (<1)
Hallucination, auditory	1 (<1)
Schizophrenia	1 (<1)
Suicidal ideation	1 (<1)
Suicide attempt	1 (<1)
Investigations	6 (1)
Blood pressure increased	1 (<1)
Electrocardiogram QRS complex prolonged	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (<1)
Electrocardiogram QT prolonged	1 (<1)
Electrocardiogram T wave abnormal	1 (<1)
Electrocardiogram T wave inversion	1 (<1)
Nervous system disorders	5 (1)
Akathisia	2 (<1)
Headache	2 (<1)
Tremor	1 (<1)
Skin and subcutaneous tissue disorders	2 (<1)
Dermatitis allergic	1 (<1)
Pruritus	1 (<1)
Rash	1 (<1)
Rash erythematous	1 (<1)
Blood and lymphatic system disorders	1 (<1)
Thrombocytopenia	1 (<1)
Eye disorders	1 (<1)
Vision blurred	1 (<1)
Gastrointestinal disorders	1 (<1)
Swollen tongue	1 (<1)
Hepatobiliary disorders	1 (<1)
Cholelithiasis	1 (<1)
Injury, poisoning and procedural complications	1 (<1)
Intentional overdose	1 (<1)
Musculoskeletal and connective tissue disorders	1 (<1)
Muscle spasms	1 (<1)
Reproductive system and breast disorders	1 (<1)
Amenorrhoea	1 (<1)
Galactorrhoea	1 (<1)

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Table 36: Treatment-Emergent Adverse Events Leading to Study Discontinuation by MedDRA Preferred Term - Double-Blind Phase (Study R076477-SCH-301: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)	Total (N=206) n (%)
Total no. subjects who discontinued due to AE	1 (1)	3 (3)	4 (2)
Vascular disorders	0	2 (2)	2 (1)
Hypertension	0	1 (1)	1 (<1)
Venous thrombosis	0	1 (1)	1 (<1)
Cardiac disorders	0	1 (1)	1 (<1)
Tachycardia	0	1 (1)	1 (<1)
Eye disorders	0	1 (1)	1 (<1)
Visual disturbance	0	1 (1)	1 (<1)
Gastrointestinal disorders	1 (1)	0	1 (<1)
Nausea	1 (1)	0	1 (<1)
Musculoskeletal and connective tissue disorders	0	1 (1)	1 (<1)
Musculoskeletal chest pain	0	1 (1)	1 (<1)
Nervous system disorders	0	1 (1)	1 (<1)
Sedation	0	1 (1)	1 (<1)

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Table 37: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=13) n (%)	Pla/Pali >6 months (N=67) n (%)	Pali/Pali <=6 months (N=2) n (%)	Pali/Pali >6 months (N=70) n (%)	Pali(NO DB)/Pali <=6 months (N=59) n (%)	Pali(NO DB)/Pali >6 months (N=24) n (%)
Total no. subjects with adverse events	3 (23)	2 (3)	0	1 (1)	3 (5)	0
Psychiatric disorders	1 (8)	1 (1)	0	1 (1)	1 (2)	0
Anxiety	0	1 (1)	0	0	0	0
Depression	0	1 (1)	0	0	1 (2)	0
Suicidal ideation	0	0	0	1 (1)	0	0
Suicide attempt	1 (8)	0	0	0	0	0
Investigations	0	1 (1)	0	0	0	0
Electrocardiogram QT prolonged	0	1 (1)	0	0	0	0
Gastrointestinal disorders	0	0	0	0	1 (2)	0
Vomiting	0	0	0	0	1 (2)	0
Nervous system disorders	2 (15)	0	0	0	1 (2)	0
Dizziness	0	0	0	0	1 (2)	0
Dyskinesia	1 (8)	0	0	0	0	0
Syncope	1 (8)	0	0	0	0	0
Tremor	1 (8)	0	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	1 (2)	0
Amenorrhoea	0	0	0	0	1 (2)	0

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 37: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Total Pali <=6 months (N=74) n (%)	Total Pali >6 months (N=161) n (%)
Total no. subjects with adverse events	6 (8)	3 (2)
Psychiatric disorders	2 (3)	2 (1)
Anxiety	0	1 (1)
Depression	1 (1)	1 (1)
Suicidal ideation	0	1 (1)
Suicide attempt	1 (1)	0
Investigations	0	1 (1)
Electrocardiogram QT prolonged	0	1 (1)
Gastrointestinal disorders	1 (1)	0
Vomiting	1 (1)	0
Nervous system disorders	3 (4)	0
Dizziness	1 (1)	0
Dyskinesia	1 (1)	0
Syncope	1 (1)	0
Tremor	1 (1)	0
Reproductive system and breast disorders	1 (1)	0
Amenorrhoea	1 (1)	0

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125

Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Total no. subjects with adverse events	10 (10)	5 (4)	30 (14)	14 (3)	18 (17)	8 (6)	58 (14)	27 (4)
Psychiatric disorders	4 (4)	4 (3)	19 (9)	9 (2)	10 (9)	5 (4)	33 (8)	18 (2)
Depression	1 (1)	1 (1)	2 (1)	3 (1)	1 (1)	1 (1)	4 (1)	5 (1)
Psychotic disorder	2 (2)	0	3 (1)	3 (1)	3 (3)	2 (1)	8 (2)	5 (1)
Anxiety	0	1 (1)	0	0	1 (1)	1 (1)	1 (<1)	2 (<1)
Insomnia	0	0	3 (1)	1 (<1)	1 (1)	1 (1)	4 (1)	2 (<1)
Acute psychosis	0	0	0	0	0	1 (1)	0	1 (<1)
Depressed mood	0	0	0	0	0	1 (1)	0	1 (<1)
Depressive symptom	0	1 (1)	0	0	0	0	0	1 (<1)
Paranoia	0	1 (1)	1 (<1)	0	0	0	1 (<1)	1 (<1)
Polydipsia psychogenic	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia	0	0	2 (1)	1 (<1)	3 (3)	0	5 (1)	1 (<1)
Suicidal ideation	1 (1)	0	1 (<1)	1 (<1)	2 (2)	0	4 (1)	1 (<1)
Aggression	0	0	0	0	1 (1)	0	1 (<1)	0
Agitation	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Alcoholism	0	0	0	0	1 (1)	0	1 (<1)	0
Confusional state	0	0	3 (1)	0	0	0	3 (1)	0
Delusion	0	0	2 (1)	0	1 (1)	0	3 (1)	0
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
Hallucination, auditory	0	0	1 (<1)	0	0	0	1 (<1)	0
Homicidal ideation	0	0	1 (<1)	0	0	0	1 (<1)	0
Hostility	0	0	1 (<1)	0	0	0	1 (<1)	0
Suicide attempt	0	0	1 (<1)	0	0	0	1 (<1)	0

Note: Percentages calculated with the number of subjects in each group as denominator.

127

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Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Nervous system disorders (continued)								
Akathisia	0	0	2 (1)	0	0	2 (1)	2 (<1)	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Dyskinesia	0	1 (1)	0	0	0	0	0	1 (<1)
Extrapyramidal disorder	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Hypertonia	0	0	0	0	0	1 (1)	0	1 (<1)
Mental impairment	0	0	0	0	0	1 (1)	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dizziness	0	0	0	0	2 (2)	0	2 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Dystonia	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Tremor	1 (1)	0	0	0	0	0	1 (<1)	0
Investigations	1 (1)	1 (1)	1 (<1)	3 (1)	2 (2)	0	4 (1)	4 (1)
Weight increased	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Alanine aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Aspartate aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood prolactin increased	0	1 (1)	0	0	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Gamma-glutamyltransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram T wave abnormal	0	0	0	0	1 (1)	0	1 (<1)	0
Hepatic enzyme increased	0	0	0	0	1 (1)	0	1 (<1)	0
Weight decreased	0	0	1 (<1)	0	0	0	1 (<1)	0

See footnotes on the first page of the table.

128

Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Reproductive system and breast disorders	0	0	2 (1)	1 (<1)	0	1 (1)	2 (<1)	2 (<1)
Erectile dysfunction	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Galactorrhoea	0	0	0	0	0	1 (1)	0	1 (<1)
Retrograde ejaculation	0	0	1 (<1)	0	0	0	1 (<1)	0
Injury, poisoning and procedural complications	1 (1)	0	2 (1)	1 (<1)	0	0	3 (1)	1 (<1)
Traumatic haematoma	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Self mutilation	1 (1)	0	0	0	0	0	1 (<1)	0
Metabolism and nutrition disorders	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Hyponatraemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Anorexia	0	0	1 (<1)	0	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Pneumonia aspiration	0	0	0	1 (<1)	0	0	0	1 (<1)
Dyspnoea	0	0	1 (<1)	0	0	0	1 (<1)	0
Cardiac disorders	1 (1)	0	3 (1)	0	2 (2)	0	6 (1)	0
Myocardial infarction	0	0	1 (<1)	0	0	0	1 (<1)	0
Myocardial ischaemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Palpitations	0	0	0	0	1 (1)	0	1 (<1)	0
Sinus tachycardia	1 (1)	0	0	0	1 (1)	0	2 (<1)	0
Tachycardia	0	0	1 (<1)	0	0	0	1 (<1)	0
Eye disorders	0	0	0	0	1 (1)	0	1 (<1)	0
Vision blurred	0	0	0	0	1 (1)	0	1 (<1)	0

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Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Gastrointestinal disorders	1 (1)	0	1 (<1)	0	3 (3)	0	5 (1)	0
Constipation	0	0	0	0	1 (1)	0	1 (<1)	0
Dysphagia	0	0	1 (<1)	0	0	0	1 (<1)	0
Nausea	0	0	0	0	1 (1)	0	1 (<1)	0
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Vomiting	0	0	0	0	2 (2)	0	2 (<1)	0
General disorders and administration site conditions	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Fatigue	0	0	1 (<1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0
Infections and infestations	1 (1)	0	1 (<1)	0	0	0	2 (<1)	0
Hepatitis A	0	0	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	1 (1)	0	0	0	0	0	1 (<1)	0
Musculoskeletal and connective tissue disorders	1 (1)	0	1 (<1)	0	2 (2)	0	4 (1)	0
Arthralgia	0	0	0	0	1 (1)	0	1 (<1)	0
Joint stiffness	1 (1)	0	0	0	0	0	1 (<1)	0
Muscle rigidity	0	0	1 (<1)	0	0	0	1 (<1)	0
Muscle twitching	0	0	0	0	1 (1)	0	1 (<1)	0
Skin and subcutaneous tissue disorders	0	0	1 (<1)	0	0	0	1 (<1)	0
Acne	0	0	1 (<1)	0	0	0	1 (<1)	0
Social circumstances	0	0	2 (1)	0	2 (2)	0	4 (1)	0
Alcohol use	0	0	1 (<1)	0	0	0	1 (<1)	0
Drug abuser	0	0	1 (<1)	0	2 (2)	0	3 (1)	0

See footnotes on the first page of the table.

Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Vascular disorders	0	0	0	0	1 (1)	0	1 (<1)	0
Hypertension	0	0	0	0	1 (1)	0	1 (<1)	0

See footnotes on the first page of the table.
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Common Adverse Events of the Integrated OL Safety Dataset

The sponsor provide several tables that were generally 20 or more pages each on common AEs (in the appendix of the SUR). In place of in-text summary tables the sponsor described the following with respect to common AEs, as copied out of this section of the SUR:

> "The most common adverse event among subjects treated with ER OROS paliperidone and placebo was insomnia, while the most common event among subjects treated with olanzapine was somnolence. Of the adverse events reported by 5% or more of the subjects in any treatment group, the following preferred terms had differences in incidence of ≥3% between the ER OROS paliperidone and other groups:
> • Headache, akathisia, somnolence, extrapyramidal disorder, dizziness, hypertonia, insomnia, psychotic disorder, depression, tachycardia, and sinus tachycardia were more

common among subjects who received ER OROS paliperidone than among those who received placebo;
• Headache, akathisia, extrapyramidal disorder, tremor, hypertonia, insomnia, anxiety, psychotic disorder, schizophrenia, depression, nausea, vomiting, tachycardia, and nasopharyngitis were more common among subjects who received ER OROS paliperidone than among those who received olanzapine;
• Somnolence and sedation were more common among subjects who received olanzapine than among those who received placebo or ER OROS paliperidone.
• The percentages of subjects reporting any adverse event and, in most cases, the percentages of subjects reporting the common adverse events were higher for subjects who received ER OROS paliperidone for >6 months than for subjects who received treatment for ≤6 months.
These results are similar to those presented in the SCS of NDA 21-999 using a cut-off date of 31 May 2005."

Laboratory Parameter Results

Laboratory trial data results of Completed Study -301:

SAEs and/or ADOs due to Laborateory-related AEs:

One subject had thrombocytopenia as an SAE and an ADO that occurred due to laboratory related AEs (as described in Section 3.2.1 of the SUR). Subject 100847 (40 year old male) was found in the line listing as the SAE and ADO due to thrombocytopenia which occurred during the stabilization OL treatment phase of this study (on Day 71 of the study and Day 15 of this study phase). No other ADOs or SAEs occurred due to laboratory related AEs in Study 301.

Statistical Descriptive Results. *Results were generally did not reveal any new remarkable findings that are not already described in this review, although the following additional observations are noted.*

Comment and Caveat. *Some of the cell sizes for a given data-point (on a given parameter in a given treatment group at a given time-point) were small such that mean values may deviate or be skewed from values at other time-points within the same treatment group (note that treatment groups are subdivided into ≤ 6months and > 6 month subgroups with respect to duration of exposure, as previously described). Consequently, cell sizes of approximately 100 subjects for a given time-point in a given treatment group are considered more valid and were the focus of this review.*

Another major limitation with all safety data from OL trials is the absence of placebo group. Yet, even in the absence of a placebo group one can examine the data to determine if the data yielded remarkable and/or unexpected signal that was not revealed in the placebo controlled short-term trials.

This updated dataset allows for examination of safety parameters over time through 1 year of exposure in contrast to the data provided in the N000 submission at which point the sample size of subject exposed to 1 year of treatment was small.

Please note the following semantics employed in sections below. The > 6 month and ≤ 6 month subgroups are also referred to as "exposure" subgroups in this review.

Laboratory trial data results of OL extension trial dataset (-702 through -705, combined):
SAEs and ADOs due to Laboratory-related AEs were the following:
The SUR describes the following SAEs due to laboratory parameter abnormalities (in 1 subject each) were: anemia, CPK increased, hyponatremia and hypokalemia

Note that one SAE was cholelithiasis was found by the undersigned reviewer, as described in Section 7.1.3.3 (under a subsection on LFTs).

Statistical Descriptive Results. *While noting the above caveats the results generally failed to reveal any new remarkable findings that differ from that already described in this review although the following additional observations are noted:*

- *Mean decreases in HgB values are typically -3.0 g/l or sometimes greater were observed during the OL longterm treatment.*

  It is also noteworthy that the olanzapine OL groups showed similar decreases in mean HgB values.

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DLAB02: Laboratory Values: Means and Mean Changes Over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base		Change from baseline					
	N	Mean	SD	Med	Min	Max	Mean (SD)	N	Mean	SE	SD	Med	Min	Max
HEMOGLOBIN (g/l)														
Pla/Pali <=6 months														
SCREENING (DB)	97	144.62	16.051	143.00	112.0	190.0								
BASELINE (DB)	98	145.72	15.811	147.00	112.0	194.0								
DAY 15 (DB)	96	146.96	15.642	147.00	108.0	191.0	145.68 (15.956)	96	1.29	0.917	8.009	1.00	-16.0	20.0
DAY 43 (DB)	59	143.37	15.974	143.00	107.0	171.0	143.47 (15.756)	59	-0.10	1.073	8.246	0.00	-24.0	18.0
END POINT (DB)	98	144.55	15.238	143.00	107.0	179.0	145.72 (15.811)	98	-1.17	0.905	8.956	0.00	-26.0	22.0
BASE (OPEN)	98	144.55	15.238	143.00	107.0	179.0	145.72 (15.811)	98	-1.17	0.905	8.956	0.00	-26.0	22.0
WEEK 12 (OPEN)	15	130.67	9.529	130.00	115.0	149.0	133.53 (12.506)	15	-2.87	2.214	8.576	-6.00	-17.0	15.0
WEEK 24 (OPEN)	56	140.41	13.863	138.00	114.0	178.0	143.09 (14.073)	56	-2.68	1.239	9.274	-3.00	-26.0	19.0
END POINT (OPEN)	62	139.44	13.759	138.00	114.0	178.0	142.50 (14.053)	62	-3.06	1.236	9.734	-3.00	-32.0	19.0
Pla/Pali >6 months														
SCREENING (DB)	134	143.22	14.415	144.50	92.0	175.0								
BASELINE (DB)	137	144.66	15.307	146.00	81.0	179.0								
DAY 15 (DB)	132	144.15	15.507	143.50	95.0	187.0	144.53 (15.422)	132	-0.38	0.618	7.105	-1.00	-21.0	16.0
DAY 43 (DB)	92	144.58	16.347	145.50	94.0	199.0	144.54 (16.370)	92	0.03	0.985	9.443	0.50	-27.0	37.0
END POINT (DB)	136	144.36	14.936	145.00	94.0	199.0	144.59 (15.343)	136	-0.23	0.749	8.740	0.50	-27.0	37.0
BASE (OPEN)	137	144.55	15.023	145.00	94.0	199.0	144.66 (15.307)	137	-0.10	0.756	8.853	0.00	-27.0	37.0
WEEK 12 (OPEN)	8	126.75	12.714	128.00	111.0	144.0	133.13 (14.096)	8	-6.38	1.413	3.998	-6.50	-11.0	-1.0
WEEK 24 (OPEN)	127	141.33	15.858	141.00	89.0	178.0	144.88 (15.434)	127	-3.55	0.925	10.420	-3.00	-44.0	25.0
WEEK 52 (OPEN)	42	138.38	15.633	138.00	102.0	169.0	139.95 (16.050)	42	-1.57	1.507	9.763	-2.50	-25.0	21.0
END POINT (OPEN)	129	140.96	15.798	140.00	98.0	178.0	144.66 (15.509)	129	-3.70	0.925	10.508	-3.00	-44.0	23.0
Pali/Pali <=6 months														
SCREENING (DB)	201	144.18	15.589	145.00	94.0	183.0								
BASELINE (DB)	205	145.75	15.771	147.00	89.0	187.0								
Pali/Pali <=6 months														
DAY 15 (DB)	200	142.46	15.555	143.00	98.0	184.0	145.67 (15.888)	199	-3.38	0.570	8.044	-3.00	-24.0	35.0
DAY 43 (DB)	150	142.14	15.147	144.50	99.0	172.0	145.66 (15.736)	149	-3.57	0.707	8.628	-4.00	-27.0	33.0
END POINT (DB)	206	142.24	15.639	145.00	99.0	174.0	145.66 (15.758)	204	-3.61	0.579	8.263	-4.00	-27.0	33.0
BASE (OPEN)	207	142.38	15.708	145.00	99.0	174.0	145.75 (15.771)	205	-3.56	0.575	8.240	-4.00	-27.0	33.0
WEEK 12 (OPEN)	10	127.00	12.138	123.00	114.0	152.0	128.90 (12.444)	10	-1.80	3.431	10.850	0.00	-30.0	8.0
WEEK 24 (OPEN)	114	143.51	16.691	145.50	84.0	181.0	146.88 (16.735)	114	-3.37	0.943	10.073	-3.00	-32.0	46.0
END POINT (OPEN)	124	142.19	16.920	144.00	84.0	181.0	145.42 (17.118)	124	-3.23	0.908	10.107	-3.00	-32.0	46.0
Pali/Pali >6 months														
SCREENING (DB)	458	142.14	15.360	142.00	80.0	182.0								
BASELINE (DB)	469	143.10	15.906	144.00	82.0	184.0								
DAY 15 (DB)	456	139.80	15.202	140.50	83.0	176.0	143.11 (15.789)	454	-3.33	0.386	8.219	-3.00	-28.0	38.0
DAY 43 (DB)	408	139.68	15.748	140.00	85.0	181.0	143.04 (15.855)	406	-3.38	0.441	8.882	-3.00	-34.0	25.0
END POINT (DB)	469	139.93	15.656	140.00	85.0	181.0	143.12 (15.934)	467	-3.21	0.409	8.840	-3.00	-34.0	25.0
BASE (OPEN)	471	139.97	15.730	140.00	85.0	181.0	143.10 (15.906)	469	-3.15	0.408	8.836	-3.00	-34.0	25.0
WEEK 12 (OPEN)	43	131.49	13.213	131.00	90.0	163.0	133.26 (13.146)	43	-1.77	1.496	9.810	-1.00	-28.0	17.0
WEEK 24 (OPEN)	423	140.99	14.290	142.00	75.0	174.0	142.73 (15.885)	420	-1.83	0.528	10.829	-2.00	-56.0	30.0
WEEK 52 (OPEN)	121	142.54	13.912	143.00	109.0	174.0	143.37 (15.079)	120	-1.23	1.008	11.044	-1.00	-31.0	41.0
END POINT (OPEN)	432	141.22	13.773	142.00	97.0	174.0	142.99 (15.847)	429	-1.63	0.499	10.334	-2.00	-36.0	41.0

- *Platelet count shows decreases that were numerically greater with 6 months or greater treatment compared to less than 6 months of Pal treatment as described in the following and as shown below (copied sections of Appendix 5.3.1).*

Mean decreases during Pal treatment appeared greater with increasing exposure over time based on numerical comparisons of the larger treatment subgroups such as the in the following subgroups (shown below with results from additional subgroups): DB Pal/OL Pal > 6 month group and total Pal > 6 month group in which mean decreases were approached over -20 1 giga/l or greater by 6 months of OL treatment and generally continued to be over -20 giga/l through OL treatment endpoint (including the 12 month time-point) as compared to mean changes that were generally less than -10 on previously time-points.

Note that mean decreases were smaller during Olanzapine DB treatment than during Pal treatment.

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DLAB02: Laboratory Values: Means and Mean Changes Over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base	Change from baseline					
	N	Mean	SD	Med	Min	Max	Mean (SD)	N	Mean	SE	SD	Med	Min	Max
PLATELETS (giga/l)														
Pla/Pali >6 months														
SCREENING (DB)	131	254.35	61.443	250.00	127.0	415.0								
BASELINE (DB)	137	262.17	70.364	256.00	62.0	434.0								
DAY 15 (DB)	130	275.10	67.372	266.00	105.0	456.0	261.72 (70.053)	130	13.38	4.307	49.110	11.50	-127.0	210.0
DAY 43 (DB)	91	273.41	76.752	272.00	96.0	507.0	265.70 (73.146)	91	7.70	5.239	49.980	3.00	-109.0	194.0
END POINT (DB)	135	274.76	77.037	259.00	91.0	507.0	262.71 (70.625)	135	12.04	4.611	53.579	8.00	-109.0	194.0
BASE (OPEN)	137	274.75	77.684	266.00	91.0	507.0	262.17 (70.364)	137	12.61	4.587	53.693	8.00	-109.0	194.0
WEEK 12 (OPEN)	8	264.63	53.573	275.50	122.0	374.0	230.25 (110.891)	8	34.38	25.507	72.145	40.00	-95.0	140.0
WEEK 24 (OPEN)	126	250.17	66.596	245.50	93.0	505.0	262.50 (71.406)	126	-12.33	5.065	56.861	-11.50	-147.0	194.0
WEEK 52 (OPEN)	42	266.33	64.505	268.00	138.0	428.0	270.57 (66.799)	42	-4.24	9.418	61.036	-3.00	-135.0	194.0
END POINT (OPEN)	129	251.84	66.523	254.00	93.0	432.0	263.72 (71.769)	129	-11.88	5.143	58.410	-10.00	-147.0	194.0
Pali/Pali <=6 months														
SCREENING (DB)	198	279.05	74.521	281.00	128.0	564.0								
BASELINE (DB)	205	288.07	79.430	283.00	131.0	543.0								
DAY 15 (DB)	199	275.09	78.876	273.00	109.0	535.0	289.43 (79.195)	198	-14.51	4.287	60.321	-8.00	-268.0	175.0
DAY 43 (DB)	148	281.15	77.454	275.00	129.0	538.0	289.43 (79.887)	148	-7.82	4.489	54.606	-3.50	-208.0	177.0
END POINT (DB)	206	281.57	81.715	275.00	109.0	638.0	288.47 (79.416)	204	-6.69	3.942	56.302	-3.50	-237.0	177.0
BASE (OPEN)	207	281.21	81.690	275.00	109.0	638.0	288.97 (79.430)	205	-6.65	3.923	56.169	-3.00	-237.0	177.0
WEEK 12 (OPEN)	10	226.20	60.716	191.50	163.0	348.0	227.90 (72.839)	10	-0.80	12.620	39.908	16.50	-79.0	48.0
WEEK 24 (OPEN)	113	284.13	76.480	282.00	136.0	526.0	294.09 (81.441)	113	-9.96	5.280	56.122	-7.00	-245.0	172.0
END POINT (OPEN)	123	279.22	76.625	277.00	136.0	526.0	288.63 (82.579)	123	-9.41	4.944	54.831	-6.00	-245.0	172.0
Pali/Pali >6 months														
SCREENING (DB)	456	277.52	79.810	266.00	91.0	691.0								
BASELINE (DB)	469	283.30	82.382	272.00	108.0	657.0								
DAY 15 (DB)	450	275.76	77.854	267.00	118.0	648.0	283.23 (82.430)	449	-7.41	2.462	52.179	-7.00	-260.0	276.0
DAY 43 (DB)	403	270.80	79.124	262.00	103.0	657.0	283.16 (82.231)	401	-12.21	2.725	54.562	-9.00	-245.0	229.0
END POINT (DB)	468	272.38	79.726	262.50	103.0	657.0	284.01 (82.058)	466	-11.49	2.482	53.570	-8.00	-245.0	229.0
BASE (OPEN)	471	271.61	80.275	262.00	103.0	657.0	283.30 (82.382)	469	-11.54	2.469	53.460	-7.00	-245.0	229.0
WEEK 12 (OPEN)	43	252.35	96.708	222.00	114.0	528.0	263.70 (90.482)	43	-11.35	10.517	68.963	-6.00	-217.0	175.0
WEEK 24 (OPEN)	419	259.79	73.683	259.00	61.0	530.0	284.53 (84.274)	416	-24.73	3.970	62.607	-21.50	-342.0	197.0
WEEK 52 (OPEN)	121	267.07	73.288	257.00	111.0	513.0	283.85 (78.297)	120	-18.74	5.200	56.958	-12.50	-257.0	112.0
END POINT (OPEN)	429	260.81	74.054	251.00	80.0	530.0	284.43 (83.764)	426	-23.85	2.989	61.685	-20.50	-342.0	197.0
Olan/Pali <=6 months														
SCREENING (DB)	104	264.37	73.841	254.00	106.0	535.0								
BASELINE (DB)	105	273.27	74.845	269.00	139.0	518.0								
DAY 15 (DB)	105	262.91	78.775	250.00	64.0	568.0	273.34 (75.081)	103	-10.09	5.711	57.961	-10.00	-169.0	177.0
DAY 43 (DB)	70	264.09	65.869	258.00	152.0	437.0	269.54 (75.296)	68	-4.66	5.694	46.953	-1.50	-125.0	122.0
END POINT (DB)	105	269.14	73.140	255.00	104.0	537.0	273.34 (75.081)	103	-3.57	5.226	53.036	-3.00	-158.0	177.0
BASE (OPEN)	107	268.60	72.366	255.00	104.0	537.0	273.27 (74.845)	105	-4.07	5.034	51.586	-2.00	-158.0	177.0
WEEK 24 (OPEN)	62	268.98	71.110	259.00	127.0	473.0	285.13 (74.919)	60	-14.82	6.338	49.096	-15.50	-143.0	128.0
END POINT (OPEN)	62	268.98	71.110	259.00	127.0	473.0	285.13 (74.919)	60	-14.82	6.338	49.096	-15.50	-143.0	128.0
Olan/Pali >6 months														
SCREENING (DB)	136	277.24	76.404	264.50	126.0	553.0								
BASELINE (DB)	139	281.72	72.668	277.00	141.0	545.0								
DAY 15 (DB)	133	282.70	72.957	269.00	105.0	539.0	284.00 (72.672)	133	-1.30	4.532	52.271	-6.00	-131.0	170.0
DAY 43 (DB)	130	285.87	79.328	266.00	134.0	512.0	286.87 (72.495)	119	-0.08	4.609	50.279	-3.00	-118.0	153.0
END POINT (DB)	137	284.17	77.200	265.00	134.0	512.0	283.47 (72.404)	136	1.49	4.255	49.617	-2.00	-118.0	153.0
BASE (OPEN)	140	282.41	77.362	262.50	134.0	512.0	281.72 (72.668)	139	1.45	4.163	49.076	-1.00	-118.0	153.0
WEEK 24 (OPEN)	127	260.47	75.137	255.00	90.0	522.0	285.70 (73.368)	125	-24.47	5.108	57.114	-25.00	-213.0	174.0
WEEK 52 (OPEN)	38	259.39	62.008	249.00	123.0	377.0	276.63 (86.076)	38	-17.24	11.251	69.358	-5.00	-212.0	71.0
END POINT (OPEN)	131	263.49	74.185	255.00	100.0	522.0	283.46 (73.631)	129	-19.19	5.293	60.115	-19.00	-212.0	174.0

Total Pall <=6 months															
SCREENING (DB)	399	272.23	72.844	267.00	89.0	564.0									
BASELINE (DB)	408	278.61	77.108	267.00	77.0	543.0									
DAY 15 (DB)	400	269.56	77.234	259.50	64.0	568.0	278.84	(77.078)	397	-9.25	2.863	57.036	-7.00	-268.0	177.0
DAY 43 (DB)	278	275.74	76.047	272.00	127.0	638.0	278.69	(78.880)	275	-2.44	3.025	50.172	-1.00	-208.0	172.0
END POINT (DB)	409	275.89	78.863	271.00	104.0	638.0	278.93	(77.185)	405	-2.68	2.653	53.382	-2.00	-237.0	177.0
BASE (OPEN)	412	275.54	78.647	271.00	104.0	638.0	278.61	(77.108)	408	-2.80	2.622	52.954	-2.00	-237.0	177.0
WEEK 12 (OPEN)	25	237.60	73.067	215.00	150.0	453.0	243.98	(65.851)	25	-5.48	8.174	40.871	-3.00	-89.0	63.0
WEEK 24 (OPEN)	231	272.17	73.332	268.00	127.0	526.0	284.22	(78.638)	229	-11.58	3.481	52.671	-8.00	-245.0	172.0
END POINT (OPEN)	247	269.86	74.232	266.00	127.0	526.0	281.67	(78.851)	245	-11.48	3.337	52.237	-8.00	-245.0	172.0
Total Pall >6 months															
SCREENING (DB)	723	273.27	76.581	263.00	91.0	691.0									
BASELINE (DB)	745	279.12	78.859	269.00	62.0	657.0									
DAY 15 (DB)	713	276.94	75.095	267.00	105.0	648.0	279.45	(78.884)	712	-2.47	1.955	52.173	-3.00	-200.0	276.0
DAY 43 (DB)	614	274.13	78.889	264.00	96.0	657.0	281.28	(79.276)	611	-6.88	2.167	53.564	-5.00	-245.0	229.0
END POINT (DB)	740	275.00	78.812	264.00	91.0	657.0	280.01	(78.684)	737	-4.79	1.975	53.619	-4.00	-245.0	229.0
BASE (OPEN)	748	274.22	79.270	263.00	91.0	657.0	279.13	(78.859)	745	-4.67	1.960	53.509	-3.00	-245.0	229.0
WEEK 12 (OPEN)	51	254.27	95.405	223.00	114.0	528.0	258.45	(93.539)	51	-4.18	9.907	70.751	-5.00	-217.0	175.0
WEEK 24 (OPEN)	672	258.11	72.685	250.50	61.0	539.0	280.58	(80.381)	667	-22.34	2.349	60.663	-20.00	-342.0	197.0
WEEK 52 (OPEN)	201	265.46	69.251	260.00	111.0	513.0	279.69	(77.412)	200	-15.41	4.264	60.296	-9.00	-257.0	194.0
END POINT (OPEN)	689	259.64	72.731	253.00	80.0	530.0	280.34	(80.073)	684	-20.71	2.328	60.874	-19.00	-342.0	197.0

- *Given the above results on outliers on low platelet count it is noted that clinically unremarkable mean decreases in reticulocyte count were observed during OL Pal treatment that appeared to be numerically larger in the over 6 month exposed total Pal subgroup compared to the 6 month and under exposed subgroup. Results below also include those from the DB Placebo/OL Pal subgroups as well to allow for treatment group and placebo versus Pal treatment comparisons.*

Studies R076477-SCH-302, R076477-SCH-303, R076477-SCH-304, and R076477-SCH-306

Output SCA302: Laboratory Values, Means and Mean Changes Over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean (SD)	N	change from baseline Mean	SE	SD	Med	Min	Max
RETICULOCYTES (%)														
Total Pall <=6 months														
BASELINE (DB)	407	1.86	0.942	1.80	0.1	14.1								
DAY 15 (DB)	394	1.85	0.767	1.80	0.1	9.2	1.82 (0.954)	321	0.01	0.047	0.833	0.00	-14.0	3.0
DAY 43 (DB)	276	1.91	1.495	1.80	0.2	26.2	1.83 (0.719)	234	0.13	0.095	1.459	0.00	-4.6	23.8
END POINT (DB)	406	2.01	1.372	1.80	0.1	41.7	1.83 (0.846)	403	0.13	0.095	1.914	0.00	-4.6	27.6
BASE (OPEN)	410	2.01	1.352	1.80	0.1	41.7	1.82 (0.842)	407	0.13	0.094	1.905	0.00	-4.6	27.6
WEEK 12 (OPEN)	25	1.63	0.852	1.30	0.2	4.1	1.64 (0.701)	25	0.09	0.353	0.764	-0.90	-1.3	1.1
WEEK 24 (OPEN)	127	1.80	0.622	1.70	0.5	4.0	1.88 (0.704)	226	-0.06	0.055	0.628	-0.80	-3.3	1.8
END POINT (OPEN)	144	1.80	0.672	1.70	0.2	6.1	1.84 (0.731)	243	-0.05	0.059	0.636	0.00	-3.3	3.3
Total Pall >6 months														
SCREENING (DB)	691	1.73	1.372	1.70	0.1	33.0								
BASELINE (DB)	734	1.80	0.951	1.80	0.1	9.2								
DAY 15 (DB)	691	1.80	1.092	1.80	0.1	18.2	1.80 (0.787)	691	0.00	0.040	1.063	0.00	-9.8	18.4
DAY 43 (DB)	591	1.76	1.247	1.80	0.1	24.2	1.80 (1.009)	588	-0.04	0.054	1.301	0.00	-9.8	24.6
END POINT (DB)	722	1.78	1.387	1.80	0.1	24.2	1.80 (0.876)	717	-0.02	0.046	1.193	0.00	-9.8	24.6
BASE (OPEN)	726	1.78	1.386	1.80	0.1	24.2	1.80 (0.871)	724	-0.02	0.044	1.184	0.00	-9.8	24.6
WEEK 12 (OPEN)	50	1.41	1.331	1.15	0.1	9.2	1.80 (1.079)	50	-0.39	0.188	1.332	-0.80	-9.3	4.0
WEEK 24 (OPEN)	661	1.70	0.979	1.60	0.1	7.6	1.79 (0.997)	477	-0.15	0.059	0.974	-0.10	-9.3	7.1
WEEK 52 (OPEN)	336	1.67	0.776	1.60	0.1	6.0	1.84 (1.064)	149	-0.15	0.076	1.048	-0.20	-8.9	3.3
END POINT (OPEN)	681	1.71	0.932	1.60	0.1	9.6	1.80 (0.954)	555	-0.11	0.059	0.979	-0.10	-8.9	7.1
Pla/Pall <=6 months														
SCREENING (DB)	95	1.66	0.662	1.60	0.1	3.6								
BASELINE (DB)	97	1.65	0.674	1.60	0.2	4.3								
DAY 15 (DB)	95	1.72	0.736	1.70	0.1	2.7	1.66 (0.681)	94	0.05	0.049	0.475	0.00	-0.9	1.4
DAY 43 (DB)	69	2.08	1.896	1.70	0.6	24.2	1.63 (0.706)	68	0.42	0.415	3.424	0.10	-1.6	23.8
END POINT (DB)	98	1.89	1.375	1.60	0.1	24.2	1.66 (0.674)	97	0.24	0.352	2.464	0.00	-1.6	23.8
BASE (OPEN)	98	1.89	1.375	1.60	0.1	24.2	1.66 (0.674)	97	0.24	0.352	2.464	0.00	-1.6	23.8
WEEK 12 (OPEN)	15	1.41	0.724	1.30	0.2	2.6	1.83 (0.725)	15	-0.03	0.142	0.551	0.10	-1.3	0.9
WEEK 24 (OPEN)	64	1.69	0.670	1.60	0.5	4.0	1.73 (0.710)	64	-0.07	0.084	0.672	-0.10	-1.9	1.8
END POINT (OPEN)	21	1.71	0.731	1.70	0.2	4.0	1.62 (0.714)	63	0.02	0.090	0.690	0.00	-1.9	1.8
Pla/Pall >6 months														
SCREENING (DB)	135	1.66	0.508	1.60	0.1	4.6								
BASELINE (DB)	133	1.67	0.508	1.70	0.1	3.6								
DAY 15 (DB)	126	1.71	0.561	1.70	0.1	4.6	1.68 (0.815)	126	0.04	0.044	0.492	0.10	-1.9	1.4
DAY 43 (DB)	90	1.64	0.220	1.60	0.1	2.3	1.61 (0.811)	88	-0.03	0.055	0.514	-0.10	-1.6	1.3
END POINT (DB)	131	1.66	0.288	1.70	0.1	4.6	1.66 (0.805)	131	-0.00	0.044	0.502	0.00	-1.6	2.3
BASE (OPEN)	133	1.67	0.508	1.70	0.1	4.6	1.67 (0.809)	133	-0.00	0.043	0.500	0.00	-1.6	2.3
WEEK 12 (OPEN)	2	0.85	0.565	0.60	0.2	2.8	0.93 (1.064)	2	-0.05	0.894	0.267	0.00	-0.8	0.4
WEEK 24 (OPEN)	134	1.67	1.299	1.60	0.1	3.6	1.60 (0.877)	128	0.07	0.100	1.052	0.00	-2.4	7.1
WEEK 52 (OPEN)	40	1.57	0.750	1.60	0.1	2.8	1.70 (0.910)	36	-0.11	0.132	0.810	-0.20	-3.0	1.1
END POINT (OPEN)	126	1.68	1.218	1.60	0.1	9.6	1.62 (0.856)	123	0.07	0.108	1.198	-0.00	-2.4	7.1

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- *Creatine kinase was inconsistently elevated (group mean increases) but also show mean decreases in some subgroups. Standard deviations were large (up to at least approximately ±883 U/l for given subgroup on a given time-point). Therefore, results are difficult to interpret.*

- *Mean increases in prolactin were observed during OL Pal treatment but these elevations generally did not increase in magnitude over time of treatment as shown in the following table (copied sections of Appendix 5.3.1).*

Output DLAB02: Laboratory Values: Means and Mean Changes Over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean (SD)	N	change from baseline Mean	SE	SD	Med	Min	Max
PROLACTIN (ng/ml)														
Pali/Pali >6 months														
SCREENING (DB)	470	41.55	48.388	25.25	2.3	385.0								
BASELINE (DB)	475	24.71	18.759	12.67	0.9	446.4								
DAY 15 (DB)	472	88.61	66.413	68.59	4.5	473.8	24.75 (38.905)	471	63.99	3.108	67.445	46.80	-260.0	436.9
DAY 36 (DB)	401	81.27	65.140	60.95	3.5	549.9	23.26 (38.167)	400	58.15	3.173	63.451	41.41	-176.5	512.1
DAY 43 (DB)	406	82.24	68.935	62.79	3.7	750.4	21.95 (32.518)	405	60.41	3.433	69.082	45.17	-248.0	713.6
END POINT (DB)	476	81.21	67.503	61.05	3.7	750.4	24.71 (38.759)	475	56.61	3.185	69.422	42.37	-248.0	713.6
BASE (OPEN)	476	80.92	67.419	60.89	3.7	750.4	24.71 (38.759)	475	56.31	3.181	69.325	42.19	-248.0	713.6
WEEK 12 (OPEN)	43	84.96	76.098	71.07	5.2	378.3	34.29 (41.072)	43	50.67	10.504	68.877	32.99	-29.2	345.4
WEEK 24 (OPEN)	432	74.86	63.312	56.83	3.9	576.0	24.39 (39.753)	432	50.48	3.116	64.771	36.25	-322.3	539.1
WEEK 52 (OPEN)	136	69.79	50.563	57.71	2.8	225.6	21.52 (24.265)	128	48.27	4.672	52.858	40.61	-133.7	213.5
END POINT (OPEN)	440	72.53	62.764	53.58	2.8	576.0	24.55 (39.564)	440	47.98	3.094	64.891	33.41	-322.3	539.1
Total Pali >6 months														
SCREENING (DB)	742	42.61	51.254	25.19	1.4	385.0								
BASELINE (DB)	753	24.77	17.605	12.68	0.9	446.4								
DAY 15 (DB)	739	64.01	64.690	41.94	1.2	473.8	24.75 (37.793)	738	39.30	2.463	66.920	22.93	-260.0	436.9
DAY 36 (DB)	614	60.11	62.948	40.56	2.5	548.9	23.94 (38.146)	613	36.23	2.567	63.568	21.20	-227.2	512.1
DAY 43 (DB)	608	60.93	65.693	40.76	2.4	750.4	22.54 (32.742)	607	38.44	2.717	66.943	21.41	-248.0	713.6
END POINT (DB)	753	57.84	63.422	37.01	2.1	750.4	24.72 (37.611)	752	33.16	2.421	66.396	17.68	-248.0	713.6
BASE (OPEN)	754	57.66	63.256	37.01	2.1	750.4	24.77 (37.605)	753	32.93	2.414	66.235	17.46	-248.0	713.6
WEEK 12 (OPEN)	51	81.43	73.811	56.59	5.2	378.3	31.78 (38.235)	51	49.65	9.351	65.778	31.17	-29.2	345.4
WEEK 24 (OPEN)	698	75.98	64.883	57.06	3.5	576.0	24.66 (38.413)	698	51.23	2.446	64.622	36.22	-322.3	539.1
WEEK 52 (OPEN)	208	71.57	64.845	54.06	1.8	593.8	23.06 (29.221)	208	48.51	4.499	63.443	38.91	-133.7	515.7
END POINT (OPEN)	709	71.76	63.266	52.44	1.8	593.8	24.72 (38.244)	709	47.05	2.425	64.559	33.38	-322.3	539.1

The Incidence of Outliers on Laboratory Parameters in the OL Extension Trial Safety dataset.
A Caveat: *comparisons between exposure subgroups (>6 month versus ≤ 6 month subgroups) could be misleading since the incidence is determined using a LOCF approach (that is, treatment groups are subdivided by duration of exposure rather than showing the groups combined with the incidence over time).*

Results are generally similar to those previously described, although the following are potentially notable or relevant findings (all other parameters not described or shown below generally had an incidence of 0-1% in the Total Pal ≤ 6month and > 6 month subgroups):

- *Lipid Profile Alterations: As previously described drug induced alterations in lipid profile appear to exist, as suggested by results taken from Table 69 of the SUR that are shown below.*
- *Outliers on High CPK levels: As previously described there were outliers on high CPK but not on low CPK levels.*
- *Outliers in Low Reticulocyte Count that appears to be greater after over 6 months exposure compared to 6 months and less exposure. Numerically greater incidence of outliers on low compared to high reticulocyte count that was generally more robust in the over 6 month exposed subgroups compared to the 6 month and under, exposed subgroup.*

  While the incidence of low reticulocyte count, appears to reflect a Pal effect (in light of similar findings in placebo controlled trials, as previously described in this review), a comparison between the exposure subgroups (over 6 months versus 6 months and under subgroups) may not reflect a true time-dependent phenomenon

with respect to duration of exposure. Although, these results together with other results described in this review are suggestive of such a greater effect over time of exposure. For example, the previously described results of mean platelet count over time within a given treatment group showed a slight (albeit clinically unremarkable) time-dependent decrease which supports the observations on the incidence of low platelet count when comparing the two exposure subgroups.

Table 69: Treatment-Emergent Markedly Abnormal Laboratory Results (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=309) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
LDL (mmol/L)	61	135	125	439	62	135	248	709
Abnormally high	3 (5)	7 (5)	7 (6)	23 (5)	5 (8)	8 (6)	15 (6)	38 (5)
Abnormally low	12 (20)	20 (15)	15 (12)	53 (12)	13 (21)	20 (15)	40 (16)	93 (13)
HDL (mmol/L)	64	135	129	442	63	136	256	713
Abnormally high	0	0	0	0	0	0	0	0
Abnormally low	1 (2)	14 (10)	12 (9)	40 (9)	6 (10)	10 (7)	19 (7)	64 (9)
Cholesterol (mmol/L)	65	135	131	446	64	136	260	717
Abnormally high	2 (3)	2 (1)	2 (2)	3 (1)	1 (2)	2 (1)	5 (2)	7 (1)
Abnormally low	0	0	0	0	0	0	0	0
Triglycerides (mmol/L)	64	135	131	446	64	136	259	717
Abnormally high	1 (2)	1 (1)	1 (1)	4 (1)	0	1 (1)	3 (1)	6 (1)
Abnormally low	0	0	0	0	0	0	0	0
Creatine kinase (U/L)	65	134	129	446	62	135	256	715
Abnormally high	1 (2)	2 (1)	2 (2)	1 (<1)	2 (3)	4 (3)	5 (2)	7 (1)
Abnormally low	0	0	0	0	0	0	0	0
Platelets (giga/L)	62	129	123	429	62	131	247	689
Abnormally high	0	0	0	0	0	0	0	0
Abnormally low	0	1 (1)	0	4 (1)	0	1 (1)	0	6 (1)
Reticulocytes (%)	61	126	123	424	60	131	244	681
Abnormally high	1 (2)	4 (3)	0	9 (2)	0	5 (4)	1 (<1)	18 (3)
Abnormally low	2 (3)	13 (10)	3 (2)	25 (6)	0	4 (3)	5 (2)	42 (6)

Vital Sign Results of Open Label Extension Trials Safety dataset (-702 throuth -05, combined)
SAEs and ADOs due to Vital Sign Parameters

The sponsor notes that the following SAEs and/or ADOs due to tachycardia or sinus tachycardia were reported and occurred in the ≥ 6 month exposure subgroups:

- *Subject 200601 (SAE and ADO)*
- *Subject 201366 (ADO)*
- *Subject 500603 (SAE and ADO)*
- *Subject 200303 (SAE)*

In-text descriptions of these subjects could not be found in the SUR. Several of these subjects were previously described in the sub-sections on SAEs 7.1.2 focusing on tachycardia in the absence of concurrent orthostatic and/or ischemia-related events.

In a separate section of the SUR focusing on orthostatic hypotension (section 2.1.6.5.2) the sponsor notes that there were no SAEs or ADOs due to orthostatic hypotension.

An in-text listing or discussion of other type of vital sign outliers, ADOs or SAEs could not be found in the SUR (e.g. due to non-postural hypotension, low heart rate or other subjects with remarkable vital signs or vital-sign related events, other than those of tachycardia and orthostatic hypotension, as above). Refer to previous summary tables for ADOs and SAEs and Section 7.1.3.3 of this review for descriptions of individual subjects found from other sources.

Descriptive Statistical Results: *These results failed to yield any new remarkable findings that are not already described in this review (see section 7.1.8 for more details on assessment time-points and on the results).*

Incidence of Outliers
Results on the incidence of outliers are generally similar to that previously described in this review and in the original NDA submission.

A Caveat: *Comparisons between exposure groups on the incidence of outliers may be misleading since the greater the number of assessments and the greater duration of monitoring subjects leads to a greater chance of detecting outliers. However, if a greater incidence is observed in the > 6 month exposure subgroup compared to the ≤ 6 month subgroup for outliers in one direction (e.g. high values) but not in the other direction (e.g. low values) on a given parameter, this finding may suggest a real time-dependent effect. However, statistical descriptive results failed to show mean increases in heart rate during OL treatment in the group of subjects that previously received DB pal treatment.*

Potentially new and notable findings (not previously described in this review) revealed from the results in the updated safety summary are the following:

- *A numerically greater incidence of decreased supine systolic BP and in decreased diastolic BP compared to the incidence of increased values on these parameters as shown in the table below (coped from Table 74 of the SUR).*
- *Small numerical trends for a greater incidence of the following cardiovascular effects of Pal in each of the > 6 month exposed subgroups compared to each of their corresponding ≤ 6 month subgroups:*
  - *Increased standing heart rate,*
  - *Decreased standing and*
  - *Decreased supine systolic BP.*

These findings may be reflective of having a greater chance of meeting outlier criteria associated with longer term monitoring of subjects. However, these trends for generally observed for almost all subgroups and the direction of vital sign changes are generally

consistent with Pal effects observed in the short-term trials. Although, short-term trials of primarily non-elderly subjects did not reveal a consistent or dose-dependent Pal effects on the incidence in decreased supine systolic BP. However, the single elderly Phase III trial that was conducted (-302) revealed a numerical trend for a greater incidence of decreased supine systolic BP in the Pal compared to placebo group (while noting this was a small study).

Table 74: Number of Subjects With Abnormal Vital Sign Values During the Open-Label Period
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 Months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Standing pulse classification	99	137	209	476	108	141	416	754
Decrease >=15 and value <=50	0	1 (1)	1 (<1)	3 (<1)	1 (1)	1 (1)	2 (<1)	4 (1)
Increase >=15 and value >=100	28 (28)	45 (33)	45 (22)	114 (24)	30 (28)	38 (27)	103 (25)	197 (26)
Supine pulse classification	99	137	209	476	108	141	416	754
Decrease >=15 and value <=50	0	6 (4)	0	16 (3)	1 (1)	4 (3)	1 (<1)	26 (3)
Increase >=15 and value >=100	14 (14)	20 (15)	24 (11)	47 (10)	18 (17)	16 (11)	56 (13)	83 (11)
Standing SBP classification	99	137	209	476	108	141	416	754
Decrease >=20 and value <=90	3 (3)	10 (7)	16 (8)	33 (7)	4 (4)	12 (9)	23 (6)	55 (7)
Increase >=20 and value >=180	0	0	1 (<1)	4 (1)	0	1 (1)	1 (<1)	5 (1)
Supine SBP classification	99	137	209	476	108	141	416	754
Decrease >=20 and value <=90	3 (3)	5 (4)	9 (4)	22 (5)	3 (3)	6 (4)	14 (3)	33 (4)
Increase >=20 and value >=180	1 (1)	0	3 (1)	2 (<1)	1 (1)	0	5 (1)	3 (<1)
Standing DBP classification	99	137	209	476	108	141	416	754
Decrease >=15 and value <=50	5 (5)	2 (1)	4 (2)	5 (1)	1 (1)	3 (2)	10 (2)	10 (1)
Increase >=15 and value >=105	3 (3)	8 (6)	5 (2)	11 (2)	3 (3)	5 (4)	11 (3)	24 (3)
Supine DBP classification	99	137	209	476	108	141	416	754
Decrease >=15 and value <=50	1 (1)	3 (2)	4 (2)	14 (3)	3 (3)	2 (1)	8 (2)	19 (3)
Increase >=15 and value >=105	1 (1)	4 (3)	5 (2)	5 (1)	0	0	6 (1)	9 (1)

Note: Percentages calculated with the number of subjects per parameter as denominator.
tsfvs06_t1.rtf generated by tsfvs06.sas.

In a separate section of the SUR focusing on orthostatic hypotension (section 2.1.6.5.2) the incidence of outliers on orthostatic hypotension is somewhat numerically larger in the table below than was previously reported and as previously described in this review, as shown below (copied from the SUR).

Table 56: Number of Subjects With Treatment-Emergent Orthostatic Hypotension at Anytime During the Open-Label Period
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Total no. subjects with orthostatic hypotension	4 (4)	9 (7)	7 (3)	30 (6)	4 (4)	7 (5)	15 (4)	46 (6)
Pulse(std-sup)>15 and DBP(std-sup)<-10	3 (3)	6 (4)	3 (1)	21 (4)	1 (1)	6 (4)	7 (2)	33 (4)
Pulse(std-sup)>15 and SBP(std-sup)<-20	1 (1)	4 (3)	6 (3)	14 (3)	3 (3)	4 (3)	10 (2)	22 (3)

Note: Percentages calculated with the number of subjects in each group as denominator.
tsfvs04_t1.rtf generated by tsfvs04.sas.

The above results also suggest a greater incidence of outliers on this parameter after over 6 months exposure compared to exposure at 6 months or under. However, in the absence of a placebo control group and given that the incidence was determined using an LOCF approach (rather than over time), the results are not considered conclusive evidence for a greater effect on the incidence of outliers on orthostatic hypotension with prolonged treatment. Despite this caveat, it is notable that in the previously shown table that the incidence of outliers on low standing SBP showed a similar pattern for greater incidence in the over 6 month exposed subgroup compared to the ≤ 6 month subgroup which was not observed in the direction of outliers for a high standing SBP. This observation is highly suggestive of a real Pal effect over time rather than an effect of greater time of monitoring independent of Pal treatment.

The results on the incidence of tachycardia-related AEs suggest a similar pattern for a numerically greater incidence in the over 6 month subgroups compared to the 6 month and under subgroups, as described in a separate section of the SUR that focuses on selected AEs including tachycardia. Results are shown below (copied from the SUR).

Table 41: Treatment-Emergent Tachycardia-Related Adverse Events By MedDRA Preferred Term - Open-Label Phase
(Studies R076477-SCH-702, 703, 704, and 705: Safety Analysis Set)

Tachycardia-Related Group Dictionary-derived Term	Pla/Pali ≤6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali ≤6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali ≤6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)
Total no. subjects with Tachycardia-Related AE	10 (10)	18 (13)	12 (6)	48 (10)	7 (6)	19 (13)
Tachycardia	10 (10)	18 (13)	12 (6)	48 (10)	7 (6)	19 (13)
Heart rate increased	1 (1)	0	0	3 (<1)	0	1 (1)
Sinus tachycardia	8 (8)	11 (8)	2 (1)	22 (5)	5 (5)	7 (5)
Tachycardia	1 (1)	9 (7)	10 (5)	35 (7)	3 (3)	11 (8)

Note: Percentages calculated with the number of subjects in each group as denominator.
tsfae33_t1.rtf generated by tsfae33.sas

Refer to the last section of this review for additional comments and recommendations.

ECG Results of Open Label Extension Trials Safety dataset (-702 throuth -05, combined)
SAEs and ADOs due to Abnormal ECG Parameters

See previous summary tables for the incidence of SAEs and ADOs due to ECG parameters.

In a separate section of the SUR focusing on orthostatic hypotension (section 2.1.6.5.2) the sponsor notes that there were no SAEs or ADOs due to orthostatic hypotension.

Descriptive Statistical Results: *The results (mean and median change from baseline) failed to yield any new remarkable findings that are not already described in this review (see section 7.1.8 for more details on assessment time-points and on the results), except for some of the following observations that were observed in subjects exposed over 6 months (noting that now the sample sizes are remarkably larger for these longer term exposures than samples sizes in the previous original NDA submission)*

A Potentially Greater Group Mean QT Prolongation Effect was Observed with Over 6 months of Treatment Compared to Mean Changes Observed with Less than 6 Months of Treatment.

QTraw interval results showed the most remarkable group mean increases at 6 month and at 1 year (52 week) time-points and showed at least trends for group mean increases at all time-points beyond the 8 week OL time-point.

The greatest group mean increase occurred at 52 weeks which was 7.2 (median increase was 11.0 msec), although the group variance was large (SD±25.2 msec) as may be expected since timing of assessments relative to dosing on a given day was not held constant.

QTraw interval results showed more remarkable prolongation effects than the QTc results. Since, ECG assessments during the OL study phase showed little to no change in HR (as shown later in this section of this review), it is appropriate to consider QTraw interval results over the QTc results. QTc interval results at these later time-points are likely to be a less accurate reflection of true drug effects on QT interval, since correction methods were employed correct for the case when alterations in HR are observed.

Also, note that RR interval (shown later in this section) unexpectedly showed group mean increases at these later time-points rather than showing the mean decreases that were observed at earlier time-points in the DB phase. These RR results are consistent with early drug effects on increasing HR, and the absence of this effect at later time-points (refer to the section below for possible explanations for the observed increases in RR interval). Also see the last section of this review for further comment and recommendations.

One concern is that OL results on QT interval (or QTc interval) are likely to be an underestimation of true QT interval effects since the timing of ECG assessments were not tightly controlled to capture peak plasma levels or were not obtained over multiple time-points on a given day to capture peak levels for a given individual. Also consider food effects and other factors impacting PK, as well as dynamic changes in the cardiovàscular system that may influence results.

While theoretically, subjects are in steady state from a PK perspective during OL longterm treatment, Pal levels nevertheless, fluctuate over time and vary widely across individuals. Moreover, levels can further be altered by factors that influence PK. For example, consider the large food effect of Pal on PK.

The following tables were copied out of appendices to the SUR for the over 6 month DB Pal/OL Pal group (this is the group with longest continuous Pal treatment of all subgroups shown in summary tables by the sponsor).

Output DEXG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
QT INTERVAL (ms)														
BASELINE (DB)	475	371.5	30.11	368.0	294	470								
AVERAGE PREDOSE	475	371.9	28.16	369.0	302	477								
DAY 4 (DB) : 4H PST	463	357.5	29.03	354.8	285	460	371.9	463	-14.5	0.99	21.26	-14.3	-103	70
DAY 4 (DB) : 10H PST	456	361.6	29.35	360.0	284	465	372.3	456	-10.7	1.08	23.06	-9.5	-128	68
DAY 4 (DB) : 22H PST	456	367.8	30.63	364.0	290	480	371.9	456	-4.1	1.06	22.63	-2.8	-99	67
DAY 8 (DB) : 4H PST	469	361.2	28.47	358.0	301	464	372.0	468	-10.8	1.04	22.54	-9.8	-87	63
DAY 8 (DB) : 10H PST	467	364.0	28.78	361.0	300	476	371.9	466	-7.9	1.08	23.30	-7.0	-99	68
DAY 8 (DB) : 22H PST	468	371.7	29.92	370.0	299	483	371.7	467	0.1	1.11	24.06	1.3	-105	69
DAY 15 (DB)	44	385.0	35.68	386.5	306	447	386.7	44	-1.7	3.68	24.40	-1.7	-44	58
DAY 15 (DB) : PRE-DS	419	370.7	29.61	369.0	287	462	370.5	418	0.1	1.17	23.89	0.9	-92	73
DAY 15 (DB) : 1-2H PST	421	361.9	29.00	359.0	284	471	370.5	420	-8.6	1.21	24.75	-7.8	-95	59
DAY 15 (DB) : 4H PST	422	360.2	28.31	359.5	287	454	370.1	421	-9.8	1.21	24.78	-9.3	-115	53
DAY 29 (DB)	450	371.9	30.21	370.0	298	475	371.8	449	0.1	1.07	22.66	-0.7	-74	58
DAY 36 (DB) : PRE-DS	369	375.6	30.93	376.0	304	457	370.2	368	5.3	1.30	25.03	3.7	-69	81
DAY 36 (DB) : 1-2H PST	370	369.7	28.12	367.0	296	444	370.3	369	-0.6	1.21	23.29	-1.0	-66	62
DAY 36 (DB) : 4H PST	363	369.8	27.79	369.0	303	457	370.6	362	-0.9	1.20	22.80	-0.7	-68	62
DAY 43 (DB)	414	376.2	29.33	374.5	307	493	372.0	413	4.1	1.14	23.10	5.0	-74	70
END POINT (DB)	476	374.8	29.33	372.0	307	493	371.9	475	2.8	1.08	23.49	4.0	-75	70
BASE (OPEN)	476	375.3	29.42	373.0	307	493	371.9	475	3.3	1.09	23.69	4.3	-75	70
DAY 4 (OPEN)	455	371.3	28.78	370.0	292	475	371.7	454	-0.4	1.13	24.04	-1.0	-77	63
WEEK 1 (OPEN)	462	372.1	28.11	371.0	305	456	372.2	461	-0.2	1.13	24.29	0.0	-98	66
WEEK 2 (OPEN)	462	371.9	29.20	372.0	294	458	371.9	461	-0.0	1.17	25.14	1.3	-69	65
WEEK 4 (OPEN)	468	372.3	29.55	370.0	282	469	372.0	468	0.3	1.19	25.48	1.4	-109	69
WEEK 8 (OPEN)	469	371.8	29.24	371.0	293	460	371.7	468	0.1	1.17	25.22	0.3	-83	79
WEEK 16 (OPEN)	470	374.0	30.66	372.0	301	479	372.1	469	1.8	1.21	26.15	1.3	-92	113
WEEK 24 (OPEN)	440	377.4	30.04	375.0	295	498	371.9	439	5.4	1.27	26.54	5.0	-83	98
WEEK 40 (OPEN)	269	372.6	29.91	369.0	296	474	369.7	268	2.9	1.61	26.32	2.2	-60	85
WEEK 52 (OPEN)	119	376.9	30.11	374.0	301	472	369.7	119	7.2	2.31	25.20	11.0	-56	80
END POINT (OPEN)	476	377.2	29.69	376.0	301	498	371.9	475	5.3	1.20	26.23	4.7	-58	85

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DEXG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
RR (ms)														
QTC INTERVAL FRIDERICIA (ms)														
Pali/Pali >6 months														
BASELINE (DB)	475	396.6	19.69	398.0	337	470								
AVERAGE PREDOSE	475	398.9	18.14	398.7	355	465								
DAY 4 (DB) : 4H PST	463	396.7	17.83	395.0	353	462	398.8	463	-2.1	0.57	12.34	-1.7	-42	39
DAY 4 (DB) : 10H PST	456	396.9	18.23	397.0	337	453	399.0	456	-2.1	0.62	13.29	-1.3	-74	44
DAY 4 (DB) : 22H PST	456	401.4	19.33	402.0	346	456	398.8	456	2.5	0.62	13.23	3.2	-37	40
DAY 8 (DB) : 4H PST	469	397.3	18.05	397.0	342	460	399.0	468	-1.6	0.64	13.93	-1.2	-59	51
DAY 8 (DB) : 10H PST	467	397.6	18.74	397.0	333	462	398.8	466	-1.2	0.67	14.52	-0.3	-71	46
DAY 8 (DB) : 22H PST	468	402.1	19.11	401.0	346	463	398.8	467	3.3	0.65	14.04	4.0	-44	63
DAY 15 (DB)	44	410.3	22.04	411.5	363	460	411.6	44	-1.3	2.18	14.46	-0.5	-35	30
DAY 15 (DB) : PRE-DS	419	397.9	18.44	397.0	350	470	397.6	418	0.2	0.65	13.30	1.2	-50	37
DAY 15 (DB) : 1-2H PST	421	393.8	17.31	393.0	350	456	397.7	420	-3.9	0.62	12.81	-4.0	-63	32
DAY 15 (DB) : 4H PST	422	394.6	17.35	395.0	332	443	397.4	421	-2.8	0.70	14.42	-2.7	-73	40
DAY 29 (DB)	450	399.0	18.71	399.0	350	469	399.0	449	-0.0	0.65	13.79	0.7	-49	34
DAY 36 (DB) : PRE-DS	369	399.3	17.17	399.0	356	465	397.7	368	1.5	0.72	13.72	1.3	-43	41
DAY 36 (DB) : 1-2H PST	370	395.6	17.60	395.0	345	457	397.6	369	-2.0	0.76	14.69	-1.7	-46	50
DAY 36 (DB) : 4H PST	363	397.0	17.20	396.0	352	462	397.5	362	-0.5	0.74	14.06	-0.5	-44	37
DAY 43 (DB)	414	399.8	19.30	399.0	344	502	398.9	413	0.8	0.70	14.25	0.7	-51	69
MAXIMUM VALUE (DB)	476	415.1	17.89	414.0	373	502	398.9	475	16.1	0.53	11.64	16.8	-19	69
END POINT (DB)	476	399.4	19.21	399.0	344	502	398.9	475	0.5	0.65	14.12	0.3	-51	69
BASE (OPEN)	476	399.7	19.29	399.0	344	502	398.9	475	0.8	0.65	14.15	1.0	-51	69
DAY 4 (OPEN)	455	398.7	19.24	398.0	343	482	398.7	454	-0.1	0.64	13.74	-0.5	-44	38
WEEK 1 (OPEN)	462	398.2	18.99	396.0	348	468	399.1	461	-0.9	0.65	13.99	0.3	-52	43
WEEK 2 (OPEN)	462	399.0	18.63	398.0	345	454	398.9	461	0.1	0.67	14.39	-0.3	-62	51
WEEK 4 (OPEN)	468	397.7	18.86	398.0	316	465	399.0	468	-1.3	0.69	14.95	-0.7	-79	41
WEEK 8 (OPEN)	469	397.6	17.90	397.0	354	459	398.8	468	-1.2	0.68	14.77	-0.5	-63	38
WEEK 16 (OPEN)	470	399.2	18.59	400.0	352	460	399.0	469	0.2	0.66	14.35	0.7	-50	40
WEEK 24 (OPEN)	440	400.9	18.78	400.0	348	487	399.0	439	2.0	0.72	15.04	1.7	-44	42
WEEK 40 (OPEN)	269	399.0	17.77	399.0	346	452	396.8	268	2.1	0.86	14.13	2.0	-50	40
WEEK 52 (OPEN)	118	399.9	18.18	399.0	342	456	397.1	119	2.8	1.32	14.42	2.3	-35	38
MAXIMUM VALUE (OPEN)	476	414.2	19.56	413.5	364	578	398.9	475	15.3	0.62	13.48	14.7	-21	137
END POINT (OPEN)	476	401.2	19.03	401.0	342	487	398.9	475	2.2	0.67	14.68	2.3	-50	40
QTC LINEAR SAGIE (ms)														

Pali/Pali >6 months														
BASELINE (DB)	475	397.6	18.82	398.0	337	469								
AVERAGE PREDOSE	475	399.9	17.13	399.7	360	464								
DAY 4 (DB) :4H PST	463	397.8	16.46	397.0	358	462	399.7	463	-1.9	0.54	11.65	-1.7	-40	35
DAY 4 (DB) :10H PST	456	398.2	16.84	397.5	338	452	399.9	456	-1.7	0.59	12.58	-1.0	-70	45
DAY 4 (DB) :22H PST	456	402.3	16.98	402.0	353	456	399.7	456	2.5	0.59	12.58	2.7	-35	60
DAY 8 (DB) :4H PST	469	398.6	16.80	398.0	337	459	399.9	468	-1.2	0.61	13.23	-1.0	-56	49
DAY 8 (DB) :10H PST	467	399.0	17.44	398.0	340	461	399.7	466	-0.7	0.64	13.76	-0.4	-66	47
DAY 8 (DB) :22H PST	468	402.9	17.84	402.0	347	461	399.7	467	3.2	0.62	13.44	3.3	-44	59
DAY 15 (DB)	44	410.4	21.10	410.0	368	461	411.9	44	-1.5	2.13	14.12	-0.3	-34	29
DAY 15 (DB) :PRE-DS	419	399.0	17.50	398.0	345	468	398.6	418	0.4	0.63	12.88	1.3	-46	36
DAY 15 (DB) :1-2H PST	421	395.2	16.18	395.0	357	455	398.6	420	-3.4	0.61	12.52	-3.5	-69	38
DAY 15 (DB) :4H PST	422	396.0	16.21	397.0	369	442	398.4	421	-2.4	0.69	14.16	-2.5	-97	38
DAY 29 (DB)	450	399.8	17.87	399.0	339	468	400.0	449	-0.1	0.63	13.36	0.7	-50	42
DAY 36 (DB) :PRE-DS	369	399.9	16.61	400.0	351	464	398.7	368	1.2	0.69	13.24	1.0	-38	40
DAY 36 (DB) :1-2H PST	370	396.7	16.84	396.0	345	456	398.6	369	-1.9	0.74	14.21	-1.3	-46	49
DAY 36 (DB) :4H PST	363	398.2	16.30	398.0	354	462	398.5	362	-0.3	0.72	13.62	0.3	-47	35
DAY 43 (DB)	414	400.7	18.46	400.0	348	500	399.8	413	0.9	0.67	13.69	1.0	-48	68
MAXIMUM VALUE (DB)	476	415.3	16.91	414.0	376	500	399.8	475	15.5	0.51	11.21	15.3	-19	68
END POINT (DB)	476	400.5	18.31	400.0	348	500	399.8	475	0.6	0.62	13.48	1.0	-48	68
BASE (OPEN)	476	400.7	18.39	400.0	348	500	399.8	475	0.9	0.62	13.52	1.3	-48	68
DAY 4 (OPEN)	455	399.7	18.34	399.0	330	479	399.6	454	0.1	0.63	13.37	0.0	-50	44
WEEK 1 (OPEN)	462	399.4	18.05	398.0	341	464	400.0	461	-0.6	0.63	13.49	0.3	-53	39
WEEK 2 (OPEN)	462	400.2	17.56	399.0	347	451	399.8	461	0.3	0.64	13.73	0.3	-62	51
WEEK 4 (OPEN)	468	398.8	18.04	399.0	319	464	399.9	468	-1.1	0.67	14.48	0.0	-76	40
WEEK 8 (OPEN)	469	398.5	17.08	398.0	352	458	399.7	468	-1.2	0.66	14.22	-0.8	-60	38
WEEK 16 (OPEN)	470	400.3	17.63	401.0	354	459	399.9	469	0.3	0.63	13.75	0.5	-48	39
WEEK 24 (OPEN)	440	401.4	18.46	401.0	337	487	399.8	439	1.6	0.71	14.80	1.7	-43	57
WEEK 40 (OPEN)	269	399.9	16.80	400.0	351	450	397.8	268	2.1	0.83	13.64	2.5	-50	37
WEEK 52 (OPEN)	119	401.1	17.40	400.0	350	456	398.2	119	2.9	1.29	14.08	3.0	-38	38
MAXIMUM VALUE (OPEN)	476	414.6	18.28	414.0	369	553	399.8	475	14.8	0.58	12.59	14.3	-20	112
END POINT (OPEN)	476	401.8	18.48	401.0	337	487	399.8	475	2.0	0.66	14.29	2.3	-48	38
QTC LINEAR DERIVED (ms)														
Pali/Pali >6 months														
BASELINE (DB)	475	395.1	18.84	397.0	337	468								
AVERAGE PREDOSE	475	398.2	17.28	398.6	358	464								
DAY 4 (DB) :4H PST	463	395.5	16.73	395.0	355	461	398.2	463	-2.6	0.54	11.60	-2.3	-41	33
DAY 4 (DB) :10H PST	456	396.2	17.13	395.0	337	451	398.3	456	-2.2	0.59	12.58	-1.7	-68	43
DAY 4 (DB) :22H PST	456	400.3	17.28	400.0	351	457	398.2	456	2.1	0.59	12.58	2.3	-37	38
DAY 8 (DB) :4H PST	469	396.5	17.02	396.0	338	459	398.3	468	-1.8	0.61	13.21	-1.5	-57	48
DAY 8 (DB) :10H PST	467	397.1	17.67	396.0	339	461	398.1	466	-1.0	0.64	13.71	-0.3	-65	45
DAY 8 (DB) :22H PST	468	401.2	18.02	400.0	347	460	398.1	467	3.1	0.62	13.49	3.7	-47	60
DAY 15 (DB)	44	409.3	21.31	408.5	365	460	410.8	44	-1.5	2.14	14.17	-1.3	-35	28
DAY 15 (DB) :PRE-DS	419	397.4	17.64	397.0	346	467	397.0	418	0.4	0.63	12.87	1.0	-48	38
DAY 15 (DB) :1-2H PST	421	393.3	16.35	392.0	355	455	397.0	420	-3.7	0.60	12.39	-3.3	-66	34
DAY 15 (DB) :4H PST	422	393.9	16.34	394.5	313	442	396.8	421	-2.8	0.68	14.00	-3.0	-91	37
DAY 29 (DB)	450	398.3	17.99	397.0	341	467	398.3	449	-0.1	0.63	13.26	0.7	-50	41
DAY 36 (DB) :PRE-DS	369	398.5	16.79	398.0	352	464	397.1	368	1.4	0.69	13.28	1.0	-40	41
DAY 36 (DB) :1-2H PST	370	395.2	16.86	394.5	345	455	396.9	369	-1.8	0.73	14.10	-1.0	-44	47
DAY 36 (DB) :4H PST	363	395.5	16.40	396.0	356	462	396.8	362	-0.3	0.71	13.49	0.3	-43	36
DAY 43 (DB)	414	399.4	18.57	398.6	347	500	398.2	413	1.1	0.67	13.66	1.3	-48	68
MAXIMUM VALUE (DB)	476	413.6	17.29	413.0	373	500	398.2	475	15.1	0.52	11.26	15.3	-20	68
END POINT (DB)	476	399.0	18.44	398.0	347	500	398.2	475	0.7	0.62	13.48	1.0	-48	68
BASE (OPEN)	476	399.3	18.52	398.5	347	500	398.2	475	1.0	0.62	13.53	1.3	-48	68
DAY 4 (OPEN)	455	398.2	18.43	398.0	331	478	398.0	454	0.1	0.63	13.32	0.0	-47	42
WEEK 1 (OPEN)	462	397.9	18.14	396.0	345	462	398.4	461	-0.6	0.63	13.47	0.0	-50	39
WEEK 2 (OPEN)	462	398.6	17.75	398.0	346	449	398.2	461	0.3	0.64	13.76	0.3	-61	50
WEEK 4 (OPEN)	468	397.3	18.16	397.0	318	463	398.3	468	-1.0	0.67	14.50	-0.2	-78	41
WEEK 8 (OPEN)	469	397.0	17.14	396.0	354	457	398.1	468	-1.1	0.66	14.21	-0.7	-61	37
WEEK 16 (OPEN)	470	398.7	17.83	399.0	354	458	398.3	469	0.4	0.63	13.68	0.7	-49	39
WEEK 24 (OPEN)	440	400.0	18.39	399.0	340	487	398.2	439	1.8	0.70	14.70	2.0	-42	53
WEEK 40 (OPEN)	269	398.3	16.97	397.0	350	451	396.1	268	2.2	0.84	13.75	2.3	-48	38
WEEK 52 (OPEN)	119	399.6	17.68	398.0	347	455	396.4	119	3.2	1.30	14.19	4.0	-35	40
MAXIMUM VALUE (OPEN)	476	413.1	18.51	412.0	367	549	398.2	475	14.9	0.58	12.60	14.3	-19	110
END POINT (OPEN)	476	400.4	18.50	399.0	340	487	398.2	475	2.1	0.66	14.34	2.0	-49	40

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base	-------- Change from average predose --------						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
QTC INTERVAL BAZETT (ms)														

Pal1/Pal1 >6 months														
BASELINE (DB)	475	410.2	23.12	411.0	337	477								
AVERAGE PREDOSE	475	413.5	20.50	414.0	359	475								
DAY 4(DB):4H PST	463	418.2	20.03	417.0	359	474	413.4	463	4.8	0.78	16.69	4.7	-41	69
DAY 4(DB):10H PST	456	416.1	20.01	416.0	339	468	413.5	456	2.6	0.80	17.11	2.2	-109	44
DAY 4(DB):22H PST	456	419.6	20.63	420.0	362	467	413.4	456	6.2	0.82	17.42	6.0	-48	64
DAY 8(DB):4H PST	469	417.0	20.29	417.0	336	476	413.6	468	3.4	0.81	17.51	3.0	-63	62
DAY 8(DB):10H PST	467	415.9	20.78	416.0	345	480	413.4	466	2.5	0.86	18.62	3.6	-72	60
DAY 8(DB):22H PST	468	418.5	22.14	418.0	346	479	413.5	467	5.1	0.85	18.31	5.3	-69	65
DAY 15(DB)	44	424.2	23.66	425.0	380	471	425.0	44	-0.8	2.70	17.92	-0.5	-35	47
DAY 15(DB):PRE-DS	419	412.7	21.74	413.0	344	483	412.1	418	0.3	0.86	17.66	1.2	-53	74
DAY 15(DB):1-2H PST	421	411.1	20.27	411.0	357	474	412.4	420	-1.3	0.89	18.20	-2.0	-78	57
DAY 15(DB):4H PST	422	413.3	20.46	414.0	313	483	412.2	421	1.1	0.95	19.57	1.3	-104	64
DAY 29(DB)	450	413.6	22.12	413.5	337	478	413.8	449	-0.1	0.88	18.55	1.0	-62	74
DAY 36(DB):PRE-DS	369	412.2	20.85	413.0	350	522	412.6	368	-0.5	0.94	18.04	-0.2	-77	63
DAY 36(DB):1-2H PST	370	409.6	21.61	408.0	344	481	412.4	369	-2.8	1.03	19.76	-2.0	-85	73
DAY 36(DB):4H PST	363	411.6	20.52	412.0	351	474	412.0	362	-0.4	0.99	18.83	0.3	-65	63
DAY 43(DB)	414	412.4	21.99	412.0	351	506	413.4	413	-1.0	0.90	18.26	-0.7	-62	77
MAXIMUM VALUE(DB)	476	437.0	18.51	436.0	386	522	413.5	475	23.4	0.67	14.57	22.5	-17	77
END POINT(DB)	476	412.7	21.89	413.0	351	506	413.5	475	-0.9	0.83	18.18	-0.3	-62	77
BASE(OPEN)	476	412.8	21.91	413.0	351	506	413.5	475	-0.7	0.83	18.19	-0.3	-62	77
DAY 4(OPEN)	455	413.5	22.48	414.0	331	498	413.4	454	0.1	0.87	18.59	0.3	-63	63
WEEK 1(OPEN)	462	412.2	21.72	411.0	339	488	413.6	461	-1.4	0.84	17.94	-1.0	-69	55
WEEK 2(OPEN)	462	413.7	21.05	414.0	349	473	413.5	461	0.2	0.85	18.22	0.0	-66	64
WEEK 4(OPEN)	468	411.5	21.77	412.0	321	478	413.7	468	-2.2	0.86	18.54	-1.0	-77	45
WEEK 8(OPEN)	469	411.7	21.91	410.0	349	471	413.4	468	-1.7	0.89	19.22	-1.3	-69	60
WEEK 16(OPEN)	470	413.0	20.99	414.0	350	474	413.5	469	-0.5	0.89	19.31	0.3	-73	67
WEEK 24(OPEN)	440	413.9	23.00	415.0	337	488	413.6	439	0.3	0.96	20.07	0.7	-67	68
WEEK 40(OPEN)	369	413.3	20.77	414.0	355	477	411.4	268	1.9	1.09	17.87	2.0	-59	58
WEEK 52(OPEN)	119	412.4	19.33	412.0	359	466	411.9	119	0.5	1.68	18.37	1.0	-66	48
MAXIMUM VALUE(OPEN)	476	432.2	21.14	433.0	378	625	413.5	475	18.7	0.79	17.11	18.0	-27	170
END POINT(OPEN)	476	414.3	22.68	415.0	337	482	413.5	475	0.7	0.88	19.17	2.0	-67	58

The following are QT and QTc interval results for the placebo/Pal group (heart rate in this group increased as expected upon switching subjects from DB placebo to OL Pal).

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DEAG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base	change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
QT INTERVAL (ms)														
Pla/Pal1 <=6 months														
BASELINE(DB)	99	372.1	30.07	372.0	320	444								
AVERAGE PREDOSE	99	372.5	29.12	370.0	317	443								
DAY 4(DB):4H PST	96	367.6	33.40	365.0	296	462	372.2	96	-4.6	2.31	22.68	-5.2	-56	44
DAY 4(DB):10H PST	95	373.1	32.62	371.0	304	492	373.5	95	-0.3	2.23	21.71	-3.0	-53	59
DAY 4(DB):22H PST	92	379.3	32.32	373.5	303	489	374.4	92	4.9	2.29	21.93	2.0	-39	61
DAY 8(DB):4H PST	98	369.2	34.52	367.0	285	463	372.5	98	-3.3	2.45	24.26	-3.0	-92	79
DAY 8(DB):10H PST	98	369.5	32.35	369.0	289	439	372.4	98	-2.9	2.17	21.45	-3.3	-60	48
DAY 8(DB):22H PST	97	376.3	32.82	376.0	297	473	372.3	97	4.0	2.10	20.71	2.0	-32	59
DAY 15(DB)	21	400.7	34.06	401.0	327	456	390.7	21	10.0	4.02	18.42	9.3	-31	55
DAY 15(DB):PRE-DS	74	369.8	31.26	371.5	312	457	368.2	74	1.6	1.40	20.62	0.0	-52	47
DAY 15(DB):1-2H PST	76	359.2	28.55	359.5	296	443	368.5	76	-9.3	2.64	23.01	-9.3	-71	41
DAY 15(DB):4H PST	76	360.3	29.73	359.5	297	438	367.7	76	-7.4	2.59	22.62	-7.3	-62	67
DAY 29(DB)	73	375.1	35.15	374.0	305	457	374.7	73	0.4	2.64	22.52	-1.7	-48	78
DAY 36(DB):PRE-DS	32	369.3	33.05	365.0	321	443	371.3	32	-2.0	3.88	21.93	-1.1	-43	39
DAY 36(DB):1-2H PST	32	361.5	28.24	356.0	313	433	369.4	32	-8.0	3.70	20.92	-8.8	-53	34
DAY 36(DB):4H PST	30	364.9	25.52	365.5	320	410	369.9	30	-5.0	3.71	20.32	-6.8	-44	43
DAY 43(DB)	50	380.6	37.04	374.5	310	474	378.1	50	2.5	3.39	23.97	-1.2	-47	60
END POINT(DB)	99	373.3	35.89	371.0	305	474	372.5	99	0.9	2.78	27.62	-0.5	-63	78
BASE(OPEN)	99	374.7	35.68	369.0	305	474	372.5	99	2.2	2.74	27.30	-0.3	-61	78
DAY 4(OPEN)	87	364.6	34.07	366.0	292	467	372.5	87	-7.9	2.64	24.62	-7.0	-64	53
WEEK 1(OPEN)	86	361.6	29.46	358.5	306	438	372.0	86	-10.4	2.63	24.36	-15.0	-59	50
WEEK 2(OPEN)	80	365.2	30.11	363.0	298	460	371.8	80	-6.6	2.68	23.95	-9.0	-75	71
WEEK 4(OPEN)	73	369.9	35.37	367.0	302	483	372.8	73	-3.0	2.96	24.81	-1.7	-62	61
WEEK 8(OPEN)	55	371.8	31.62	365.0	306	463	371.5	55	0.3	3.52	26.08	2.0	-47	62
WEEK 16(OPEN)	26	380.6	31.94	379.5	332	465	377.5	26	3.1	4.95	25.25	6.2	-65	45
WEEK 24(OPEN)	11	383.1	35.70	387.0	310	435	386.2	11	-3.1	10.44	34.64	4.0	-47	48
END POINT(OPEN)	99	373.5	36.35	368.0	294	483	372.5	99	1.0	2.73	27.18	2.7	-70	61

Pla/Pal1 >6 months														
BASELINE (DB)	137	371.9	26.33	372.0	310	451								
AVERAGE PREDOSE	137	370.4	25.27	367.0	316	442								
DAY 4 (DB) :4H PST	135	366.8	28.05	368.0	286	433	370.6	135	-3.8	1.92	22.35	-3.7	-89	50
DAY 4 (DB) :10H PST	135	367.3	29.50	369.0	284	434	370.7	135	-3.4	2.25	26.19	-1.7	-96	64
DAY 4 (DB) :22H PST	136	376.4	30.53	378.5	304	456	370.5	136	6.0	2.20	25.67	6.3	-79	71
DAY 8 (DB) :4H PST	136	366.9	26.19	368.5	306	425	370.6	136	-3.7	2.20	25.68	-3.0	-93	67
DAY 8 (DB) :10H PST	135	371.4	27.95	369.0	293	439	370.9	135	0.4	2.34	27.15	-1.3	-96	75
DAY 8 (DB) :22H PST	135	378.1	29.34	379.0	294	458	370.5	135	7.6	2.28	26.47	10.7	-98	65
DAY 15 (DB)	9	391.8	23.56	401.0	351	425	388.5	9	3.3	9.95	29.86	2.7	-28	74
DAY 15 (DB) :PRE-DS	127	374.7	28.00	376.0	305	441	368.9	127	5.8	2.30	25.89	7.0	-109	80
DAY 15 (DB) :1-2H PST	127	365.9	27.66	367.0	291	432	369.0	127	-3.1	2.38	26.84	-1.0	-87	85
DAY 15 (DB) :4H PST	128	368.3	28.91	370.5	294	450	369.1	128	-0.8	2.28	25.77	1.8	-86	77
DAY 29 (DB)	118	371.0	29.62	370.0	294	452	372.1	118	-1.1	2.55	27.68	1.8	-115	69
DAY 36 (DB) :PRE-DS	84	375.5	32.30	372.0	297	458	368.6	84	6.9	2.98	27.30	8.5	-84	74
DAY 36 (DB) :1-2H PST	83	367.9	27.26	372.0	302	438	369.4	83	-1.5	2.79	25.44	0.5	-83	59
DAY 36 (DB) :4H PST	85	368.9	29.12	370.0	312	455	368.9	85	0.1	3.11	28.67	3.0	-64	110
DAY 43 (DB)	91	377.0	32.62	379.0	310	459	370.7	91	6.2	2.64	25.20	9.0	-58	86
END POINT (DB)	137	373.7	30.54	375.0	306	459	370.4	137	3.4	2.31	26.99	8.3	-115	86
BASE (OPEN)	137	374.0	30.54	376.0	306	459	370.4	137	3.6	2.31	27.03	8.3	-115	86
DAY 4 (OPEN)	131	357.4	31.12	356.0	283	424	370.6	131	-13.2	2.29	26.23	-11.7	-100	65
WEEK 1 (OPEN)	130	361.1	26.38	357.5	303	443	370.6	130	-9.5	2.10	23.91	-8.3	-82	58
WEEK 2 (OPEN)	130	364.1	26.94	364.0	306	454	370.8	130	-6.8	2.17	24.78	-6.7	-96	54
WEEK 4 (OPEN)	132	368.8	29.02	368.0	305	461	370.1	132	-1.3	2.29	26.36	-1.3	-62	71
WEEK 8 (OPEN)	133	369.9	28.43	368.0	287	466	370.3	133	-0.4	2.01	23.23	-2.3	-67	53
WEEK 16 (OPEN)	132	369.2	26.90	369.5	294	432	370.5	132	-1.3	2.18	25.00	-2.0	-73	54
WEEK 24 (OPEN)	129	373.3	28.57	373.0	309	484	370.1	129	3.2	2.46	27.89	2.7	-92	72
WEEK 40 (OPEN)	80	372.1	30.64	368.5	318	443	368.7	80	3.5	2.94	26.27	2.3	-84	59
WEEK 52 (OPEN)	40	374.7	28.31	370.5	313	421	369.8	40	4.8	4.72	29.86	10.0	-66	64
END POINT (OPEN)	137	375.2	30.22	375.0	313	484	370.4	137	4.9	2.47	28.92	5.3	-84	72

The placebo/Pal results for QTc interval are only shown for the over 6 month exposure subgroup since sample sizes were larger than in the ≤ 6 month exposure subgroup.

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DECG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base	change from average predose						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
QTC INTERVAL BAZETT (ms)														
Pla/Pal1 >6 months														
BASELINE (DB)	137	406.9	23.60	408.0	342	468								
AVERAGE PREDOSE	137	408.0	20.52	407.0	339	455								
DAY 4 (DB) :4H PST	135	407.3	21.60	408.0	353	485	408.5	135	-1.2	1.35	15.67	-2.7	-42	53
DAY 4 (DB) :10H PST	135	406.8	21.31	409.0	341	451	407.9	135	-1.1	1.56	18.14	-1.0	-59	74
DAY 4 (DB) :22H PST	136	406.6	22.96	406.5	346	460	408.1	136	-1.5	1.31	15.31	-3.0	-45	47
DAY 8 (DB) :4H PST	136	405.8	22.65	407.0	335	456	408.0	136	-2.3	1.43	16.72	-2.3	-59	62
DAY 8 (DB) :10H PST	135	405.1	23.26	403.0	340	455	408.0	135	-2.8	1.49	17.24	-3.5	-48	59
DAY 8 (DB) :22H PST	135	407.4	24.29	407.0	348	459	408.0	135	-0.6	1.60	18.63	-0.5	-63	75
DAY 15 (DB)	9	424.8	21.11	420.0	404	469	428.1	9	-3.4	5.83	17.49	-7.7	-19	41
DAY 15 (DB) :PRE-DS	127	404.6	22.80	407.0	336	455	406.3	127	-1.7	1.53	17.24	-1.0	-56	51
DAY 15 (DB) :1-2H PST	127	402.6	23.49	401.0	344	468	406.7	127	-4.1	1.67	18.80	-2.7	-54	68
DAY 15 (DB) :4H PST	128	404.4	22.65	407.0	338	462	406.6	128	-2.2	1.69	19.10	0.0	-63	55
DAY 29 (DB)	118	408.7	23.66	407.5	361	461	408.3	118	0.3	1.77	19.26	0.2	-49	65
DAY 36 (DB) :PRE-DS	84	405.9	26.87	403.5	345	486	406.7	84	-0.8	2.28	20.88	-0.6	-45	58
DAY 36 (DB) :1-2H PST	83	405.8	24.03	407.0	339	471	406.8	83	-1.0	2.26	20.63	1.0	-63	73
DAY 36 (DB) :4H PST	85	404.0	24.20	404.0	347	470	406.7	85	-2.7	2.10	19.36	-1.0	-49	72
DAY 43 (DB)	91	406.1	22.53	408.0	330	473	407.5	91	-1.4	1.62	15.45	-2.3	-34	51
MAXIMUM VALUE (DB)	137	428.1	31.08	429.0	363	486	408.0	137	20.1	1.38	16.11	19.0	-25	75
END POINT (DB)	137	408.1	23.52	408.0	330	473	408.0	137	0.1	1.64	19.14	-0.7	-49	65
BASE (OPEN)	137	408.0	23.26	408.0	330	473	408.0	137	0.0	1.64	19.23	-1.0	-49	65
DAY 4 (OPEN)	131	416.3	22.15	417.0	352	464	408.0	131	8.3	1.51	17.28	8.7	-39	66
WEEK 1 (OPEN)	130	415.4	23.15	416.5	345	469	407.8	130	7.5	1.64	18.73	10.0	-51	54
WEEK 2 (OPEN)	130	411.5	20.27	415.0	351	450	407.8	130	3.7	1.45	16.54	4.7	-59	64
WEEK 4 (OPEN)	132	408.8	20.93	409.0	328	451	408.2	132	0.6	1.61	18.53	1.5	-52	77
WEEK 8 (OPEN)	133	410.0	21.54	412.0	341	472	407.8	133	2.2	1.50	17.33	1.3	-41	51
WEEK 16 (OPEN)	132	410.1	22.63	412.5	348	474	408.1	132	2.0	1.65	18.98	1.8	-52	66
WEEK 24 (OPEN)	129	411.6	22.22	412.0	347	463	408.5	129	2.4	1.72	19.53	3.7	-54	48
WEEK 40 (OPEN)	80	412.9	23.10	412.5	370	463	406.8	80	6.1	2.36	21.14	6.0	-51	52
WEEK 52 (OPEN)	40	415.9	18.31	420.0	385	449	407.1	40	8.7	2.64	16.68	6.5	-24	53
MAXIMUM VALUE (OPEN)	137	431.2	17.76	432.0	386	474	408.0	137	23.2	1.27	14.85	22.3	-13	77
END POINT (OPEN)	137	410.8	21.54	411.0	347	463	408.0	137	2.8	1.76	19.94	2.0	-47	66

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DESG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
QTC INTERVAL FRIDERICIA (ms)														
Pla/Pali >6 months														
BASELINE (DB)	137	394.8	19.23	393.0	347	452								
AVERAGE PREDOSE	137	394.9	17.33	394.0	347	444								
DAY 4 (DB) :4H PST	135	393.1	17.92	393.0	359	467	395.3	135	-2.1	1.08	12.58	-2.7	-40	48
DAY 4 (DB) :10H PST	135	393.0	18.43	393.0	350	441	394.9	135	-2.0	1.29	15.05	-1.3	-46	56
DAY 4 (DB) :22H PST	136	396.0	19.79	395.0	353	459	395.0	136	1.1	1.22	14.22	1.5	-37	44
DAY 8 (DB) :4H PST	136	392.1	18.24	391.5	338	433	395.0	136	-2.8	1.15	13.36	-3.0	-41	40
DAY 8 (DB) :10H PST	135	393.3	18.87	392.0	346	443	395.1	135	-1.7	1.18	13.73	-3.3	-41	45
DAY 8 (DB) :22H PST	135	397.1	19.69	399.0	337	438	394.9	135	2.2	1.22	14.22	2.5	-47	59
DAY 15 (DB)	9	413.3	14.80	416.0	386	435	414.3	9	-1.0	5.51	16.54	-4.7	-20	29
DAY 15 (DB) :PRE-DS	127	394.0	17.28	395.0	339	439	393.2	127	0.8	1.13	12.69	0.5	-36	43
DAY 15 (DB) :1-2H PST	127	389.7	18.70	390.0	335	432	393.5	127	-3.8	1.24	14.00	-3.3	-37	52
DAY 15 (DB) :4H PST	128	391.6	17.48	392.0	329	438	393.5	128	-1.9	1.15	13.07	-1.7	-42	39
DAY 29 (DB)	118	395.5	19.57	394.0	350	452	395.7	118	-0.2	1.28	13.87	-0.3	-46	52
DAY 36 (DB) :PRE-DS	84	395.2	20.80	392.5	343	457	393.4	84	1.8	1.64	15.03	-2.6	-31	40
DAY 36 (DB) :1-2H PST	83	392.4	17.81	391.0	339	442	393.7	83	-1.3	1.55	14.09	-1.5	-36	31
DAY 36 (DB) :4H PST	85	391.7	19.18	392.0	344	446	393.5	85	-1.8	1.50	13.86	-3.0	-35	48
DAY 43 (DB)	91	395.8	19.22	396.0	332	445	394.7	91	1.1	1.30	12.40	1.3	-27	40
MAXIMUM VALUE (DB)	137	411.4	18.01	412.0	362	467	394.9	137	16.5	1.08	12.68	15.3	-14	59
END POINT (DB)	137	396.0	18.60	396.0	332	445	394.9	137	1.1	1.19	13.97	0.7	-27	52
BASE (OPEN)	137	396.0	18.58	396.0	332	445	394.9	137	1.1	1.21	14.14	0.7	-27	52
DAY 4 (OPEN)	131	395.4	19.48	395.0	343	442	395.0	131	0.5	1.23	14.04	-0.3	-30	36
WEEK 1 (OPEN)	130	396.3	18.23	395.5	342	446	394.9	130	1.4	1.21	13.77	2.0	-32	36
WEEK 2 (OPEN)	130	394.8	16.76	395.0	353	427	394.9	130	-0.1	1.16	13.20	-0.2	-33	51
WEEK 4 (OPEN)	132	394.7	16.71	395.0	348	437	394.9	132	-0.2	1.13	13.01	-0.5	-31	38
WEEK 8 (OPEN)	133	395.9	18.27	395.0	351	455	394.7	133	1.2	1.07	12.37	-0.3	-31	43
WEEK 16 (OPEN)	132	395.7	18.72	394.5	353	458	395.0	132	0.7	1.24	14.28	2.0	-35	55
WEEK 24 (OPEN)	129	397.6	17.31	398.0	353	466	395.1	129	2.5	1.24	14.04	3.0	-39	33
WEEK 40 (OPEN)	80	398.3	17.40	396.5	363	443	393.5	80	4.8	1.74	15.52	6.7	-42	32
WEEK 52 (OPEN)	40	401.4	16.30	399.0	368	437	394.2	40	7.2	2.45	15.50	5.7	-25	36
MAXIMUM VALUE (OPEN)	137	411.3	16.28	410.0	360	466	394.9	137	16.4	0.97	11.34	17.0	-9	55
END POINT (OPEN)	137	398.2	17.61	395.0	360	466	394.9	137	3.3	1.34	15.67	3.0	-42	55

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DESG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
QTC LINEAR SAGIE (ms)														
Pla/Pali >6 months														
BASELINE (DB)	137	395.8	18.85	395.0	344	452								
AVERAGE PREDOSE	137	396.0	16.74	395.3	340	444								
DAY 4 (DB) :4H PST	135	394.4	17.37	395.0	357	463	396.4	135	-2.0	1.05	12.16	-2.0	-36	48
DAY 4 (DB) :10H PST	135	394.4	18.05	394.0	342	441	396.0	135	-1.6	1.26	14.62	-0.3	-42	57
DAY 4 (DB) :22H PST	136	396.9	19.46	397.0	348	459	396.6	136	0.8	1.17	13.61	0.3	-39	41
DAY 8 (DB) :4H PST	136	393.5	18.01	393.0	335	434	396.1	136	-2.5	1.11	13.00	-3.0	-44	41
DAY 8 (DB) :10H PST	135	394.4	18.77	393.0	342	443	396.1	135	-1.7	1.16	13.49	-3.5	-36	46
DAY 8 (DB) :22H PST	135	397.6	19.37	400.0	345	437	396.0	135	1.6	1.19	13.88	1.3	-45	58
DAY 15 (DB)	9	413.4	12.96	414.0	390	431	415.0	9	-1.5	4.86	14.59	-4.3	-19	25
DAY 15 (DB) :PRE-DS	127	394.4	18.13	397.0	331	438	394.3	127	0.1	1.16	13.05	-0.3	-42	45
DAY 15 (DB) :1-2H PST	127	391.1	17.93	392.0	343	432	394.6	127	-3.6	1.17	13.24	-3.3	-35	53
DAY 15 (DB) :4H PST	128	392.5	17.21	393.5	334	437	394.6	128	-2.1	1.12	12.66	-1.7	-41	41
DAY 29 (DB)	118	396.5	18.74	396.0	356	452	396.7	118	-0.2	1.23	13.40	-1.6	-42	48
DAY 36 (DB) :PRE-DS	84	395.2	20.17	393.5	345	451	394.5	84	0.7	1.64	15.07	-2.3	-39	36
DAY 36 (DB) :1-2H PST	83	393.3	17.29	392.0	346	441	394.7	83	-1.4	1.58	14.41	-2.0	-36	27
DAY 36 (DB) :4H PST	85	392.5	18.63	392.0	348	444	394.6	85	-2.1	1.54	14.21	-2.0	-39	46
DAY 43 (DB)	91	396.5	18.84	398.0	332	442	395.7	91	0.8	1.32	12.58	0.3	-26	45
MAXIMUM VALUE (DB)	137	411.8	17.06	412.0	363	463	396.0	137	15.8	1.02	11.96	14.7	-12	58
END POINT (DB)	137	396.6	18.15	397.0	332	442	396.0	137	0.7	1.16	13.62	0.0	-27	48
BASE (OPEN)	137	396.7	18.12	397.0	332	442	396.0	137	0.7	1.17	13.70	0.0	-27	48
DAY 4 (OPEN)	131	396.5	18.22	395.0	348	441	396.0	131	0.5	1.18	13.48	0.0	-30	34
WEEK 1 (OPEN)	130	397.2	17.08	397.5	343	443	395.9	130	1.3	1.17	13.29	2.3	-32	38
WEEK 2 (OPEN)	130	396.1	16.05	397.0	354	427	396.0	130	0.1	1.12	12.82	-0.2	-39	52
WEEK 4 (OPEN)	132	395.6	16.42	397.0	325	434	396.0	132	-0.4	1.14	13.14	0.0	-52	37
WEEK 8 (OPEN)	133	397.1	17.61	396.0	343	455	395.8	133	1.3	1.09	12.52	0.5	-30	48
WEEK 16 (OPEN)	132	396.9	17.94	396.0	348	456	396.1	132	0.8	1.21	13.88	1.0	-33	56
WEEK 24 (OPEN)	129	398.3	16.97	398.0	350	467	396.2	129	2.1	1.23	13.94	3.0	-37	40
WEEK 40 (OPEN)	80	398.7	16.65	397.5	369	442	394.9	80	3.9	1.77	15.85	5.0	-45	31
WEEK 52 (OPEN)	40	402.4	15.43	401.0	373	438	395.7	40	6.7	2.41	15.27	3.8	-28	38
MAXIMUM VALUE (OPEN)	137	411.8	15.48	410.0	366	467	396.0	137	15.8	0.97	11.33	16.0	-10	56
END POINT (OPEN)	137	398.8	17.29	396.0	350	467	396.0	137	2.9	1.34	15.64	3.0	-41	56

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DBCG01: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	Change from average predose N	Mean	SE	SD	Med	Min	Max
QTC LINEAR DERIVED (ms)														
Pla/Pal1 >6 months														
BASELINE (DB)	137	394.4	18.67	393.0	345	451								
AVERAGE PREDOSE	137	394.5	16.71	394.0	342	443								
DAY 4 (DB) :4H PST	135	392.8	17.33	393.0	358	462	394.9	135	-2.0	1.05	12.17	-2.0	-36	48
DAY 4 (DB) :10H PST	135	392.8	18.07	392.0	344	440	394.6	135	-1.7	1.26	14.60	-1.3	-41	54
DAY 4 (DB) :22H PST	136	395.7	19.39	395.5	349	458	394.6	136	1.1	1.18	13.79	0.3	-37	40
DAY 8 (DB) :4H PST	136	391.9	17.88	391.5	335	433	394.6	136	-2.7	1.12	13.07	-3.0	-42	38
DAY 8 (DB) :10H PST	135	393.1	18.64	392.0	343	442	394.7	135	-1.6	1.17	13.54	-3.0	-37	44
DAY 8 (DB) :22H PST	135	396.4	19.25	399.0	342	435	394.5	135	1.9	1.19	13.80	2.0	-42	56
DAY 15 (DB)	9	412.4	12.87	414.0	388	430	414.0	9	-1.5	4.85	14.55	-4.7	-19	23
DAY 15 (DB) :PRE-DS	127	393.3	17.83	395.0	336	439	392.9	127	0.5	1.15	12.92	0.0	-41	43
DAY 15 (DB) :1-2H PST	127	389.6	17.82	391.0	341	431	393.1	127	-3.5	1.17	13.20	-3.0	-33	51
DAY 15 (DB) :4H PST	128	391.1	17.09	392.5	333	435	393.1	128	-2.1	1.10	12.42	-1.8	-40	39
DAY 29 (DB)	118	395.0	18.73	394.5	354	452	395.3	118	-0.3	1.23	13.38	-0.7	-43	47
DAY 36 (DB) :PRE-DS	84	394.0	19.95	392.0	345	448	393.0	84	1.0	1.62	14.84	-1.7	-37	36
DAY 36 (DB) :1-2H PST	83	392.0	16.98	390.0	340	440	393.3	83	-1.3	1.55	14.08	-2.3	-34	29
DAY 36 (DB) :4H PST	85	391.2	18.42	391.0	347	445	393.1	85	-1.9	1.53	14.11	-1.3	-37	51
DAY 43 (DB)	91	395.3	18.82	397.0	332	439	394.2	91	1.0	1.32	12.63	1.3	-24	43
MAXIMUM VALUE (DB)	137	410.4	17.28	410.0	362	462	394.5	137	15.9	1.03	12.07	15.0	-11	56
END POINT (DB)	137	395.3	18.00	396.0	332	439	394.5	137	0.8	1.16	13.53	0.0	-24	47
BASE (OPEN)	137	395.3	17.99	396.0	332	439	394.5	137	0.8	1.16	13.62	0.0	-24	47
DAY 4 (OPEN)	131	394.3	18.44	392.0	347	440	394.6	131	-0.2	1.19	13.64	-0.7	-29	34
WEEK 1 (OPEN)	130	395.3	17.05	395.0	343	441	394.5	130	0.8	1.16	13.20	1.0	-32	35
WEEK 2 (OPEN)	130	394.3	16.14	394.5	355	426	394.5	130	-0.2	1.12	12.82	-0.7	-36	50
WEEK 4 (OPEN)	132	394.2	16.48	395.0	328	436	394.5	132	-0.3	1.13	12.98	-0.3	-48	37
WEEK 8 (OPEN)	133	395.5	17.71	394.0	344	455	394.4	133	1.2	1.07	12.33	0.0	-29	46
WEEK 16 (OPEN)	132	395.3	17.89	394.5	349	455	394.6	132	0.7	1.20	13.76	1.0	-33	54
WEEK 24 (OPEN)	129	396.9	16.92	397.0	352	468	394.7	129	2.2	1.21	13.75	3.0	-35	36
WEEK 40 (OPEN)	80	397.1	16.57	395.0	366	440	393.3	80	3.8	1.75	15.63	5.0	-43	31
WEEK 52 (OPEN)	40	400.8	15.71	398.5	370	437	394.1	40	6.6	2.46	15.57	4.3	-31	36
MAXIMUM VALUE (OPEN)	137	410.1	15.70	409.0	364	468	394.5	137	15.6	0.96	11.25	16.0	-8	54
END POINT (OPEN)	137	397.5	17.30	395.0	352	468	394.5	137	3.0	1.32	15.50	3.0	-43	54

RR Interval Results

RR interval results below show mean increases at later time-points that were numerically greater at 52 weeks (mean increase of 27.6 msec). These mean increases were not associated with corresponding changes in HR (as shown in the ECG HR results below). Yet heart rate is provide in units of bpm, while RR interval is provided in msec. It is difficult to interpret these results from a clinical perspective but the results may be reflecting Pal effects on QT and PR (combined) as described in the following. The RR prolongation was associated with at least trends for QT prolongation, but note that weeks 4, 8 and 16 show mean RR prolongation of approximately 8 or 9 msec while mean QT prolongation was negligible to small (0.3 to up to 2 msec). Note that a small mean PR prolongation was also observed at these time-points that may be contributing in part, to the results on RR interval. Only results of the DB Pal/OL pal over 6 month subgroup are shown below (the group that represents the longest continuous Pal exposure).

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DEC002: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	Mean	SE	SD	Med	Min	Max
								change from average predose						
HR (ms)														
BASELINE (DB)	475	831.0	155.55	800.0	462	1429								
AVERAGE PREDOSE	475	819.2	136.89	796.7	484	1429								
DAY 4 (DB) : 4H PST	467	737.9	133.62	714.0	484	1395	819.3	467	-81.4	5.58	120.48	-81.7	-543	378
DAY 4 (DB) : 10H PST	458	761.8	134.04	750.0	508	1304	820.4	458	-58.5	5.91	126.42	-57.8	-674	384
DAY 4 (DB) : 22H PST	460	776.1	144.20	759.0	504	1304	818.9	460	-42.7	5.81	124.57	-33.5	-471	353
DAY 8 (DB) : 4H PST	472	757.0	129.15	741.0	462	1277	818.5	471	-61.7	5.57	120.95	-56.0	-525	270
DAY 8 (DB) : 10H PST	468	772.8	131.14	750.0	488	1304	820.1	467	-47.1	5.90	127.49	-45.7	-498	342
DAY 8 (DB) : 22H PST	471	798.1	144.62	789.0	465	1364	818.9	470	-21.0	6.16	133.45	-16.6	-520	381
DAY 15 (DB)	44	835.1	163.14	827.5	531	1176	836.7	44	-1.6	19.02	126.14	-16.2	-186	276
DAY 15 (DB) : PRE-DS	421	815.7	147.44	800.0	496	1277	817.6	420	-1.7	6.58	134.77	-4.0	-454	422
DAY 15 (DB) : 1-2H PST	423	784.0	146.28	759.0	496	1500	817.3	422	-33.5	7.21	148.18	-36.5	-559	454
DAY 15 (DB) : 4H PST	424	767.8	140.59	750.0	417	1429	816.5	423	-48.7	7.08	145.65	-46.3	-739	582
DAY 29 (DB)	450	819.1	155.92	794.5	500	1364	817.3	449	1.5	6.20	131.41	-6.0	-442	432
DAY 36 (DB) : PRE-DS	370	842.4	163.37	833.0	368	1395	815.7	369	26.8	7.27	139.73	18.3	-366	421
DAY 36 (DB) : 1-2H PST	371	824.9	149.85	822.0	432	1277	816.7	370	8.4	7.03	135.22	6.3	-380	417
DAY 36 (DB) : 4H PST	367	814.4	141.68	800.0	444	1277	818.0	366	-3.5	6.83	130.68	-6.6	-347	404
DAY 43 (DB)	420	838.6	143.26	833.0	531	1364	818.9	419	19.4	6.27	128.27	28.7	-491	428
END POINT (DB)	476	832.6	142.10	827.5	526	1364	819.2	475	13.2	6.00	130.70	23.3	-491	428
BASE (OPEN)	475	834.3	141.88	833.0	526	1364	819.3	474	14.8	6.04	131.48	24.3	-491	428
DAY 4 (OPEN)	456	815.4	144.11	800.0	504	1364	818.3	455	-3.1	6.57	140.12	-0.3	-478	487
WEEK 1 (OPEN)	463	822.2	134.73	811.0	500	1395	819.7	462	2.3	6.26	134.58	7.8	-618	483
WEEK 2 (OPEN)	462	816.7	140.63	800.0	517	1364	818.9	461	-2.4	6.31	135.49	0.3	-446	428
WEEK 4 (OPEN)	469	827.6	148.53	811.0	465	1395	818.5	469	9.0	6.32	136.93	6.0	-435	499
WEEK 8 (OPEN)	470	827.0	154.62	811.0	462	1395	818.4	469	8.2	6.43	139.30	6.0	-448	526
WEEK 16 (OPEN)	470	823.5	152.35	811.0	522	1395	820.2	469	9.1	6.99	151.44	-0.3	-445	628
WEEK 24 (OPEN)	442	844.8	164.57	833.0	465	1500	819.2	441	25.3	7.42	155.72	19.3	-506	731
WEEK 40 (OPEN)	269	822.8	150.82	811.0	504	1277	818.0	268	5.1	8.71	142.60	11.7	-477	456
WEEK 52 (OPEN)	119	843.0	141.37	811.0	583	1176	815.4	119	27.6	12.73	138.86	22.0	-378	390
END POINT (OPEN)	476	840.1	155.08	822.0	517	1500	819.2	475	21.1	6.77	147.51	17.3	-477	598

PR Interval Results

Clinically unremarkable group mean and median increases in PR interval is observed (as shown below).

Output DEC002: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	Mean	SE	SD	Med	Min	Max
								change from average predose						
PR INTERVAL (ms)														
Pali/Pali >6 months														
BASELINE (DB)	475	151.6	19.92	150.0	95	227								
AVERAGE PREDOSE	475	151.8	19.87	150.3	92	236								
DAY 4 (DB) : 4H PST	465	151.9	20.79	151.0	100	240	151.9	465	-0.0	0.47	10.10	0.0	-38	39
DAY 4 (DB) : 10H PST	457	154.3	22.03	152.0	104	257	151.9	457	2.4	0.52	11.08	2.0	-26	75
DAY 4 (DB) : 22H PST	460	150.8	20.87	150.0	102	232	151.8	460	-1.0	0.48	10.25	-1.3	-44	36
DAY 8 (DB) : 4H PST	471	153.4	20.72	151.0	94	228	151.8	470	1.1	0.49	10.61	1.0	-32	46
DAY 8 (DB) : 10H PST	468	154.4	20.69	153.0	92	220	151.8	467	2.6	0.52	11.14	2.7	-39	38
DAY 8 (DB) : 22H PST	471	152.0	20.83	150.0	84	230	151.7	470	0.3	0.52	11.17	0.2	-41	41
DAY 15 (DB)	44	158.7	21.84	153.5	128	215	162.9	44	-4.2	2.06	13.69	-2.7	-49	16
DAY 15 (DB) : PRE-DS	421	151.5	19.93	150.0	94	223	150.5	420	0.9	0.53	10.94	0.7	-46	49
DAY 15 (DB) : 1-2H PST	422	150.6	20.73	148.0	90	272	150.6	421	-0.1	0.56	11.45	-0.3	-43	84
DAY 15 (DB) : 4H PST	423	150.6	19.98	150.0	94	216	150.7	422	-0.2	0.52	10.62	-0.3	-45	45
DAY 29 (DB)	450	152.0	20.60	150.0	89	228	151.7	449	0.3	0.52	10.94	0.3	-34	40
DAY 36 (DB) : PRE-DS	370	150.6	20.68	148.0	96	215	150.2	369	0.4	0.61	11.70	0.0	-45	60
DAY 36 (DB) : 1-2H PST	371	150.1	20.14	148.0	91	216	150.2	370	-0.1	0.58	11.20	0.6	-48	42
DAY 36 (DB) : 4H PST	365	149.9	20.65	148.0	102	228	150.3	364	-0.5	0.62	11.90	0.0	-46	63
DAY 43 (DB)	417	153.3	20.71	152.0	108	237	151.7	416	1.6	0.53	10.82	1.7	-50	29
END POINT (DB)	476	153.3	20.88	152.0	108	237	151.8	475	1.5	0.51	11.07	1.3	-50	39
BASE (OPEN)	475	153.1	20.88	152.0	108	237	151.8	475	1.3	0.51	11.10	1.3	-50	39
DAY 4 (OPEN)	456	152.3	20.67	151.0	94	260	151.7	455	0.6	0.57	12.11	0.0	-50	42
WEEK 1 (OPEN)	462	152.6	21.25	150.0	89	257	151.6	461	1.0	0.56	12.00	0.3	-51	58
WEEK 2 (OPEN)	462	152.5	20.55	151.0	107	226	151.6	461	0.9	0.56	12.06	1.0	-39	73
WEEK 4 (OPEN)	469	152.7	21.68	151.0	97	257	151.6	469	1.1	0.58	12.60	1.0	-63	80
WEEK 8 (OPEN)	470	153.3	20.64	150.0	105	225	151.7	469	1.6	0.53	11.44	2.0	-58	39
WEEK 16 (OPEN)	470	153.6	21.42	152.0	105	238	151.6	469	2.0	0.57	12.36	1.3	-31	85
WEEK 24 (OPEN)	440	152.4	22.02	150.0	91	233	151.3	439	1.0	0.62	13.01	1.7	-43	83
WEEK 40 (OPEN)	269	152.2	20.90	150.0	102	210	149.8	268	2.3	0.76	12.37	1.7	-46	56
WEEK 52 (OPEN)	119	150.9	19.08	149.0	104	197	150.7	119	0.2	1.21	13.24	-1.7	-34	47
END POINT (OPEN)	476	152.8	21.40	151.0	102	233	151.8	475	1.0	0.57	12.43	1.0	-46	47

Heart Rate Results

Results of only the DB-Pal/OL-Pal (Pali/Pali) subgroups with over 6 months exposure are shown below (as provided by the sponsor), since this group represents the subgroup with the longest exposure (since they had DB Pal as well as OL Pal). Heart rate shows little to not change during OL Pal treatment in this subgroup.

As previously discussed, failure to show a positive finding in the OL safety dataset could be associated with aspects of the study design, such as the flexible dose, non-placebo controlled design, and also consider potential between subject variance on the timing of assessments and dosing in these outpatients. The OL trials were not designed to capture time-dependent and PK-dependent effects of Pal. Refer to a previous discussion about assessment time-windows, such as in Section 7.1 X of this review.

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DBXC02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base	change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med.	Min	Max
HEART RATE (beats/min)														
Pali/Pali <=6 months														
BASELINE(DB)	209	76.7	15.25	77.0	46	149								
AVERAGE PREDOSE	209	77.3	13.56	77.0	49	134								
DAY 4(DB):4H PST	204	86.1	14.89	86.0	51	128	77.6	204	8.6	0.84	11.96	8.7	-21	54
DAY 4(DB):10H PST	198	85.5	15.06	85.5	50	130	77.4	198	8.1	0.86	12.17	7.7	-27	54
DAY 4(DB):22H PST	197	81.7	15.29	82.0	44	120	77.8	197	3.8	0.90	12.65	2.7	-32	48
DAY 8(DB):4H PST	207	83.7	13.97	85.0	52	121	77.2	207	6.5	0.82	11.79	6.0	-29	46
DAY 8(DB):10H PST	202	82.9	14.01	83.0	51	117	77.1	202	5.8	0.84	11.96	4.7	-33	40
DAY 8(DB):22H PST	207	80.3	15.86	81.0	44	128	77.2	207	3.1	0.90	12.94	2.3	-35	48
DAY 15(DB)	14	74.2	16.28	77.0	46	114	71.3	14	2.9	2.60	9.74	2.3	-14	15
DAY 15(DB):PRE-DS	193	79.6	16.27	78.0	38	123	77.8	193	1.8	0.89	12.30	1.0	-35	41
DAY 15(DB):1-2H PST	188	82.9	15.72	83.0	44	140	77.7	188	5.3	1.03	14.92	4.3	-52	61
DAY 15(DB):4H PST	187	85.0	15.86	85.0	49	137	78.0	187	7.0	1.06	14.52	5.3	-40	54
DAY 29(DB)	177	77.0	13.65	75.0	48	117	77.1	177	-0.1	1.04	13.77	0.0	-51	36
DAY 36(DB):PRE-DS	130	76.2	14.31	75.0	44	138	78.1	130	-1.9	1.17	13.31	-1.3	-39	28
DAY 36(DB):1-2H PST	130	78.5	13.14	78.5	44	115	77.9	130	0.6	1.22	13.91	0.3	-46	32
DAY 36(DB):4H PST	128	78.9	13.03	78.0	39	108	77.9	128	1.0	1.23	14.58	1.7	-52	41
DAY 43(DB)	144	75.2	13.35	74.0	47	121	77.5	144	-2.3	1.08	12.96	-1.6	-52	37
END POINT(DB)	209	76.7	14.31	76.0	47	121	77.3	209	-0.7	0.93	13.43	-0.7	-52	43
BASE(OPEN)	209	76.2	14.03	76.0	47	121	77.3	209	-1.1	0.88	12.71	-0.8	-52	37
DAY 4(OPEN)	178	77.5	14.14	75.0	47	119	77.2	178	0.3	0.98	13.05	-1.0	-37	37
WEEK 1(OPEN)	187	78.5	14.17	79.0	45	133	77.2	187	1.3	0.84	11.44	2.0	-38	26
WEEK 2(OPEN)	167	76.8	13.96	76.0	50	139	77.3	167	-0.6	0.99	12.77	0.3	-43	29
WEEK 4(OPEN)	152	76.6	14.61	75.5	44	124	76.6	152	0.0	0.99	12.20	0.2	-43	39
WEEK 8(OPEN)	103	75.0	14.72	73.0	43	110	75.7	103	-0.7	1.36	13.79	0.0	-36	34
WEEK 16(OPEN)	32	76.4	13.36	75.0	51	106	77.1	32	-0.7	2.79	15.79	-3.2	-28	45
END POINT(OPEN)	203	78.6	15.40	78.0	50	139	77.3	203	1.3	0.96	13.71	1.0	-43	45

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DESC02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	change from average predose Mean	SE	SD	Med	Min	Max
HEART RATE (beats/min)														
Pali/Pali >6 months														
BASELINE (DB)	475	74.6	13.31	75.0	42	130								
AVERAGE PREDOSE	475	75.8	12.13	76.3	42	125								
DAY 4 (DB) :4H PST	467	83.8	14.06	84.0	43	124	75.8	467	8.0	0.65	11.80	8.0	-32	48
DAY 4 (DB) :10H PST	458	81.1	13.60	80.0	46	118	75.7	458	5.4	0.57	12.16	5.7	-40	55
DAY 4 (DB) :22H PST	460	79.8	14.07	79.0	46	119	75.8	460	4.0	0.57	12.19	2.7	-29	50
DAY 8 (DB) :4H PST	472	81.5	13.36	81.0	47	130	75.8	471	5.7	0.53	11.57	5.3	-26	37
DAY 8 (DB) :10H PST	469	79.8	12.93	80.0	46	123	75.7	467	4.1	0.56	12.10	4.0	-37	41
DAY 8 (DB) :22H PST	471	77.6	13.72	76.0	44	129	75.8	470	1.8	0.59	12.74	0.8	-28	60
DAY 15 (DB)	44	74.6	15.01	72.5	51	113	73.7	44	0.9	1.78	11.82	1.3	-27	22
DAY 15 (DB) :PRE-DS	421	76.0	13.91	75.0	47	121	76.0	420	0.0	0.62	12.77	-0.3	-39	52
DAY 15 (DB) :1-2H PST	423	79.1	14.11	79.0	40	121	76.0	422	3.1	0.67	13.86	3.0	-44	44
DAY 15 (DB) :4H PST	424	80.7	14.20	80.0	42	144	76.1	423	4.6	0.67	13.79	4.0	-38	66
DAY 29 (DB)	450	75.8	13.84	75.5	44	120	75.9	449	-0.1	0.57	12.09	0.0	-40	46
DAY 36 (DB) :PRE-DS	370	74.0	15.06	72.0	43	163	76.1	369	-2.1	0.70	13.41	-2.0	-51	75
DAY 36 (DB) :1-2H PST	371	75.2	13.77	73.0	47	139	76.0	370	-0.9	0.67	12.88	-1.2	-42	53
DAY 36 (DB) :4H PST	367	75.9	13.18	75.0	47	135	75.9	366	0.0	0.65	12.39	0.0	-37	47
DAY 43 (DB)	420	73.7	12.74	72.0	44	113	75.7	419	-2.0	0.57	11.75	-2.7	-34	34
END POINT (DB)	475	74.2	12.82	72.5	44	114	75.8	475	-1.6	0.55	12.02	-2.3	-37	37
BASE (OPEN)	475	74.0	12.82	72.0	44	114	75.8	475	-1.7	0.56	12.11	-2.7	-37	37
DAY 4 (OPEN)	456	75.8	13.08	75.0	44	119	75.8	455	0.0	0.60	12.85	0.0	-41	42
WEEK 1 (OPEN)	463	75.0	12.50	74.0	43	120	75.7	462	-0.7	0.58	12.49	-1.3	-52	51
WEEK 2 (OPEN)	462	75.6	13.06	75.0	44	116	75.8	461	-0.1	0.60	12.89	-0.7	-49	51
WEEK 4 (OPEN)	469	74.8	13.23	74.0	43	129	75.8	469	-1.0	0.59	12.78	-1.0	-40	42
WEEK 8 (OPEN)	470	75.1	14.14	74.0	43	130	75.8	469	-0.7	0.61	13.17	-0.7	-43	50
WEEK 16 (OPEN)	470	74.7	13.27	74.0	43	115	75.7	469	-1.0	0.63	13.54	-0.3	-46	51
WEEK 24 (OPEN)	442	73.6	13.94	72.0	40	129	75.9	441	-2.2	0.66	13.83	-2.0	-53	45
WEEK 40 (OPEN)	269	75.4	13.82	74.0	47	119	75.9	268	-0.5	0.81	13.33	-1.3	-38	41
WEEK 52 (OPEN)	119	73.2	12.27	74.0	51	103	76.0	119	-2.9	1.14	12.40	-2.7	-34	28
END POINT (OPEN)	475	73.8	13.46	73.0	40	116	75.8	475	-2.0	0.62	13.44	-2.0	-53	34

QRS Axis showed a mean decrease of up to -4.2 degrees (±13.8) in the Pali/Pali > 6 month subgroup observed at week 52 and showed at least trends for a group mean decrease on most assessment time-points (this subgroup was selected for the focus of this review due to larger sample sizes of subjects with over 6 months exposure, as previously described).

Incidence of Outliers

Reviewer Comment: *Tables and figures of results are shown after providing the following overall comments.*

The results on overall incidence of outliers on ECG parameters failed to show any new findings that are not already described in this review (see the first table below for results). However, QT interval outlier results are based on absolute values of 500 msec or greater.

The following new finding is revealed by the longer term dataset in the SUR, when the data is examined more closely (using less stringent outlier criteria, when showing scatterplots of individual values or when examining the incidence of outliers on the change of QT interval from a pre-dose averaged value):

- *The subgroups with longer exposure (the ≥6 months) and in particular the treatment groups with continuous antipsychotic exposure (the Pal/Pal and Olanzapine/Pal subgroups) appear to exhibit the following. These groups have subjects with greater QTc values or greater changes in values from the pre-dose averaged value than subgroups with less exposure (the < 6 month subgroups). Small trends for this pattern can be seen with scatterplots of maximal QTc interval values. A small overall upward rather than a downward shift of the scatterplot (towards higher QTc values rather than*

lower QTc values) appears to exist in the ≥ 6month group compared to each corresponding < 6month exposed subgroup. Refer to the scatterplot below of "maximum QTcLD" (Table 14)

A pattern for an overall upward shift of subjects on QTc values (rather than no shift or a downward shift) appears to be more predominant when examining the results of the incidence of subjects showing a change from lower to higher QTc interval values. Refer to Table 15 below of the scatterplot of the "change of QTcLD." These results show a trend for more subjects with higher values or greater shifts are seen in the subgroups with longer Pal exposure (comparing <6 month to ≥ 6 month subgroups). This trend appears to be greatest among the subgroup exposed the longest to continuous Pal treatment which is the ≥6 month DB Pal/OL Pal subgroup and among the ≥ 6month Total Pal group (the total Pal group includes all subjects receiving OL Pal, independent of DB study drug assignment, such that a subgroup of these subjects were the ≥ 6 month DB Pal/OL pal group). These results are shown below.

A caveat to the above observations is that results may not reflect a time-dependent effect since the longer a given subject is observed the greater the likelihood a given subject will eventually show a shift or high QTc interval value. However, when examining descriptive statistical results a greater effects were observed at time-points of 6 moths and over during the OL phase. Furthermore, an examination of the individual scatterplots of QTc values appear to show an overall upward shift of QT interval in the over (such that, not only does there appear to be more subjects with higher QTc values in the ≥ 6 month subgroups, but there also appears to be fewer subjects with lower QTc values in these subgroups compared to the corresponding < 6 month subgroups). Consequently the results on the incidence may be reflecting a true Pal effect for greater QT prolongation effects over time. It may be helpful to examine the incidence of outliers at each assessment time-point (using an OC approach) and to examine the incidence of outliers with decreased or low QTc values. This additional information may be helpful in revealing results that could suggest that the above observations of the ≥ 6 month versus < 6 month subgroups may be reflection a greater incidence of outliers as a function of time and frequency of ECG monitoring versus a true drug effect. In the absence of placebo group the interpretation of results are limited, but are suspicious of a drug effect that was observed in the shorter-term placebo controlled trials that continues with longer term treatment. See the final section of this review for comments and recommendations.

Another caveat to consider regarding the sponsor's results, is that shift tables and scatterplot results were only provided for either QTcLD and/or for QTc using other additional methods. QTcF and QTcB methods (and possibly QTlc, sagie method) may be least accurate since HR did not appeared to show minimal to no change when ECG assessments were conducted (as previously described). Perhaps QTcLD is a better measure, but this measure incorporates drug-free QT/RR data.

QTraw interval results may be more accurate (due to minimal to no HR changes on the ECG assessments). However, similar tables and figures for QTraw results could not be found with these other in-text tables of the QTcLD results in the SUR that are shown below.

Finally the scatterplot tables only show results with respect to maximal QTc values, whereas a scatterplot of median values may be more appropriate depending on the frequency distribution of QT values. Furthermore, showing individual scatterplots for each treatment group but with the exposure subgroups, combined, yet showing results over time (at assessment each time-point) may a more accurate way of showing the results.

Table 84: Number of Subjects With Treatment-Emergent Abnormal ECG Values During the Open-Label Period
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

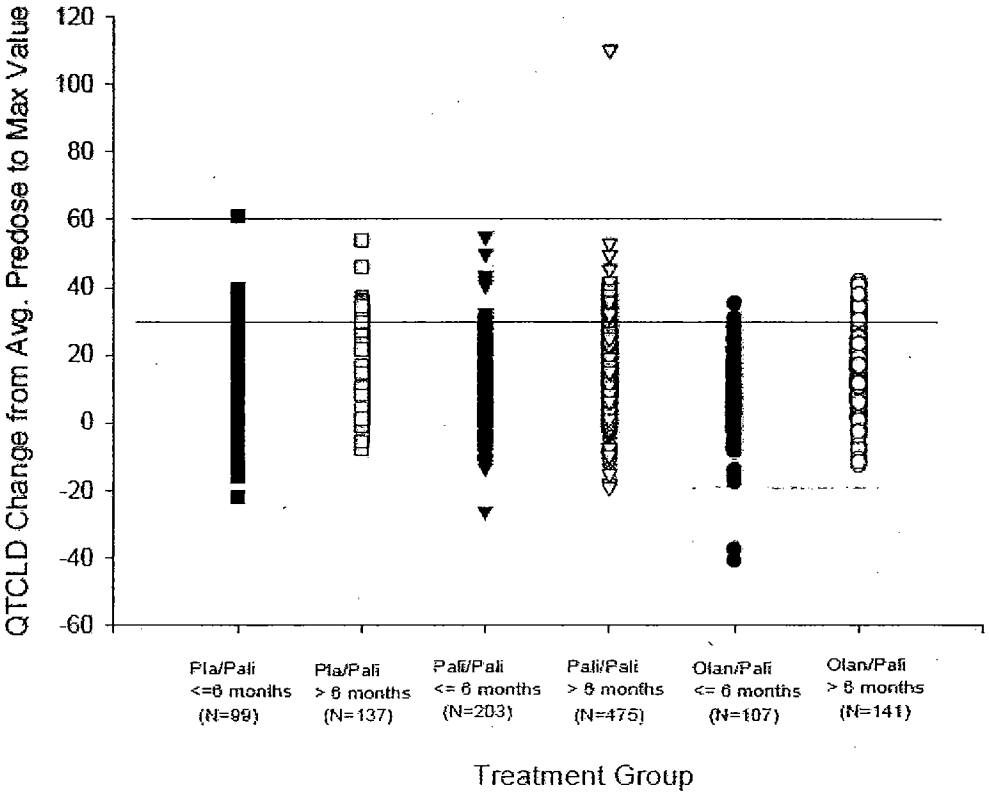
	Pla/Pali ≤6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali ≤6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali ≤6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali ≤6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Heart rate	99	137	203	476	107	141	409	754
Abnormally high	30 (30)	38 (28)	32 (16)	95 (20)	32 (30)	36 (26)	94 (23)	169 (22)
Abnormally low	2 (2)	14 (10)	7 (3)	35 (7)	4 (4)	7 (5)	13 (3)	56 (7)
PR interval	98	137	202	476	107	141	407	754
Abnormally high	0	4 (3)	1 (<1)	12 (3)	1 (1)	2 (1)	2 (<1)	18 (2)
Abnormally low	0	0	0	0	0	0	0	0
QRS interval	99	137	203	476	107	141	409	754
Abnormally high	2 (2)	1 (1)	1 (<1)	2 (<1)	1 (1)	0	4 (1)	3 (<1)
Abnormally low	0	0	0	0	0	0	0	0
QT interval	99	137	203	476	107	141	409	754
Abnormally high	0	0	0	0	0	0	0	0
Abnormally low	0	0	0	0	0	0	0	0

Note: Percentages calculated with the number of subjects per parameter as denominator.
Note: Heart rate: abnormally low: <=50 bpm, abnormally high: >=100 bpm.
PR interval: abnormally high: >=210 msec.
QRS interval: abnormally low: <=50 msec, abnormally high: >=120 msec.
QT interval: abnormally low: <=200 msec, abnormally high: >=500 msec.
tsfecg06_tsfecg.rtf generated by tsfecg.sas.

The sponsor's focus was on showing results of QTcLD, as in the following scatterplots rather than showing the below scatterplots for QT raw intervals or for QTc interval using other correction methods (these scatterplots were copied from the submission). Reviewer comments of these results were provided

abov

Figure 15: Change in QTcLD From Average Predose Value to Maximum Value During Open-Label Treatment (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)



Note: The subject with a change of more than 100 ms, who also had a maximum value greater than 500 ms, was Subject 201418; a narrative for this subject is presented at the end of this section, following Table 92.

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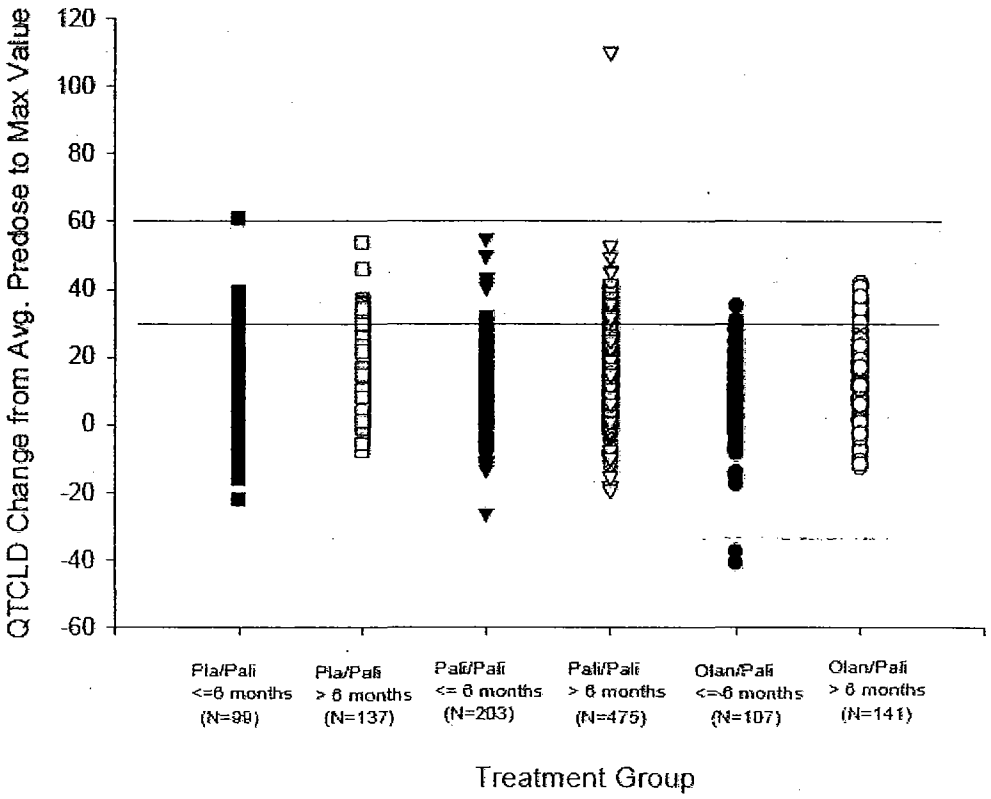
Figure 15: Change in QTcLD From Average Predose Value to Maximum Value During Open-Label Treatment (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)



Note: The subject with a change of more than 100 ms, who also had a maximum value greater than 500 ms, was Subject 201418; a narrative for this subject is presented at the end of this section, following Table 92.

The following are results of the number or incidence of subjects that met categorical shift criteria (as specified in the tables) for QTc interval using different correction methods. Similar tables for raw QT interval were not found among these in-text summary tables.

The results of DB Pal/OL Pal subgroups were copied below from the sponsor's in-text summary tables since this group of subjects received the longest continuous Pal exposure. Results of Total Pal groups are also shown (includes all subgroup regardless of their DB treatment assignment).

Table 91: Classification of Maximum Corrected QT Intervals During Open-Label Treatment Versus Average Predose Value (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Treatment Group and Evaluation at Average Predose								
	Pali/Pali <=6 months (N=209)				Pali/Pali >6 months (N=476)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD								
Maximum value								
Normal	198	0	0	198	462	1	0	463
>=450 - <480	3	2	0	5	6	4	0	10
>=480	0	0	0	0	1	1	0	2
Total	201	2	0	203	469	6	0	475
QTcF								
Maximum value								
Normal	198	0	0	198	458	1	0	459
>=450 - <480	3	2	0	5	10	3	0	13
>=480	0	0	0	0	1	2	0	3
Total	201	2	0	203	469	6	0	475
QTIc								
Maximum value								
Normal	198	0	0	198	460	1	0	461
>=450 - <480	3	2	0	5	8	4	0	12
>=480	0	0	0	0	1	1	0	2
Total	201	2	0	203	469	6	0	475
QTcB								
Maximum value								
Normal	184	1	0	185	396	4	0	400
>=450 - <480	12	5	0	17	57	15	0	72
>=480	0	1	0	1	0	3	0	3
Total	196	7	0	203	453	22	0	475

Note: Normal(Norm)(<450 ms); >=450 ms - <480 ms(>=450); >=480 ms(>=480)

Table 91: Classification of Maximum Corrected QT Intervals During Open-Label Treatment Versus Average Predose Value (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	--- Total Pali <=6 months --- (N=416)				--- Total Pali >6 months --- (N=754)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD								
Maximum value								
Normal	401	0	0	401	737	1	0	738
>=450 - <480	5	2	0	7	9	4	0	13
>=480	0	1	0	1	1	1	0	2
Total	406	3	0	409	747	6	0	753
QTcF								
Maximum value								
Normal	400	0	0	400	733	1	0	734
>=450 - <480	6	2	0	8	13	3	0	16
>=480	0	1	0	1	1	2	0	3
Total	406	3	0	409	747	6	0	753

	--- Total Pali <=6 months --- (N=416)				--- Total Pali >6 months --- (N=754)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTIc								
Maximum value								
Normal	401	0	0	401	734	1	0	735
>=450 - <480	5	2	0	7	12	4	0	16
>=480	0	1	0	1	1	1	0	2
Total	406	3	0	409	747	6	0	753
QTcB								
Maximum value								
Normal	365	1	0	366	633	6	0	639
>=450 - <480	31	8	0	39	90	20	0	110
>=480	1	3	0	4	0	4	0	4
Total	397	12	0	409	723	30	0	753

While the above tables generally do not reveal exposure subgroup differences and QTcB and QTcF results are likely to be least informative (since heart rate showed little to no change during OL treatment note the following results from the table below (as found in the submission).

Note that the incidence of outliers for greater shift categories 30 msec and over 60 msec categories, is greater in the > 6 month than the ≤ 6 month exposure subgroups. While this may be reflecting an effect of greater monitoring time-points in the latter subgroup over the former

subgroup rather than an effect of duration of Pal exposure, results on mean QTraw increases suggests QT prolongation occurring after 6 months of treatment compared time-points prior to 6 months of treatment.

Table 92: Distribution of Maximum Changes From Average Predose Value in Corrected QT Values (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
QTcLD	99	137	203	475	107	141	409	753
<30 (ms)	90 (91)	121 (88)	192 (95)	422 (89)	104 (97)	128 (91)	386 (94)	671 (89)
30-60 (ms)	8 (8)	16 (12)	11 (5)	52 (11)	3 (3)	13 (9)	22 (5)	81 (11)
>60 (ms)	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
QTcF	99	137	203	475	107	141	409	753
<30 (ms)	88 (89)	118 (86)	193 (95)	418 (88)	102 (95)	128 (91)	383 (94)	664 (88)
30-60 (ms)	10 (10)	19 (14)	10 (5)	56 (12)	5 (5)	13 (9)	25 (6)	88 (12)
>60 (ms)	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
QTlc	99	137	203	475	107	141	409	753
<30 (ms)	90 (91)	120 (88)	194 (96)	423 (89)	103 (96)	129 (91)	387 (95)	672 (89)
30-60 (ms)	8 (8)	17 (12)	9 (4)	51 (11)	4 (4)	12 (9)	21 (5)	80 (11)
>60 (ms)	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
QTcB	99	137	203	475	107	141	409	753
<30 (ms)	76 (77)	100 (73)	167 (82)	369 (78)	83 (78)	107 (76)	326 (80)	576 (76)
30-60 (ms)	20 (20)	34 (25)	35 (17)	100 (21)	23 (21)	33 (23)	78 (19)	167 (22)
>60 (ms)	3 (3)	3 (2)	1 (<1)	6 (1)	1 (1)	1 (1)	5 (1)	10 (1)

Note: Percentages calculated with the number of subjects per parameter as denominator.
tsfecg04_tsfecg.rtf generated by tsfecg.sas.

Body Weight Results

The following table summarizes body weight results of the OL trial safety dataset (as found in the SUR).

Table 77: Body Weight and BMI: Change From Baseline to End Point
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 months (N=99)	Pla/Pali >6 months (N=137)	Pali/Pali <=6 months (N=209)	Pali/Pali >6 months (N=476)	Olan/Pali <=6 months (N=108)	Olan/Pali >6 months (N=141)	Total Pali <=6 months (N=416)	Total Pali >6 months (N=754)
Weight (kg)								
N	73	64	158	240	80	54	311	358
Mean baseline (SD)	75.0 (20.13)	75.8 (18.96)	77.0 (23.46)	74.5 (19.56)	81.9 (22.51)	72.0 (14.57)	77.8 (22.55)	74.4 (18.77)
Mean change (SD)	0.3 (4.34)	0.9 (6.57)	1.5 (4.77)	1.7 (6.31)	1.4 (5.59)	3.3 (5.12)	1.2 (4.91)	1.8 (6.21)
Weight percent change (%)								
N	73	64	158	240	80	54	311	358
Mean baseline (SD)	75.0 (20.13)	75.8 (18.96)	77.0 (23.46)	74.5 (19.56)	81.9 (22.51)	72.0 (14.57)	77.8 (22.55)	74.4 (18.77)
Mean change (SD)	0.7 (5.82)	1.8 (8.67)	1.9 (6.17)	2.6 (7.93)	2.2 (7.10)	4.7 (7.20)	1.7 (6.35)	2.8 (7.99)
Body mass index (kg/m2)								
N	73	64	158	240	80	53	311	357
Mean baseline (SD)	26.5 (6.31)	26.7 (5.82)	26.4 (6.88)	26.7 (6.64)	27.5 (6.76)	24.7 (4.92)	26.7 (6.72)	26.4 (6.30)
Mean change (SD)	0.1 (1.55)	0.3 (2.32)	0.5 (1.63)	0.6 (2.25)	0.5 (1.80)	1.1 (1.72)	0.4 (1.66)	0.6 (2.20)

Baseline is double-blind baseline.
tsfvs08_t1.rtf generated by tsfvs08.sas.

Table 78: Body Weight and BMI: Change From Baseline to End Point by Region for Total ER OROS Paliperidone Group
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Region: Eastern Europe		Region: North America	
	Total Pali <=6 months (N=141)	Total Pali >6 months (N=420)	Total Pali <=6 months (N=166)	Total Pali >6 months (N=140)
Weight (kg)				
N	106	223	118	63
Mean baseline (SD)	72.9 (17.87)	71.3 (13.22)	90.7 (23.27)	94.1 (24.35)
Mean change (SD)	-0.1 (3.74)	1.4 (4.58)	2.2 (6.11)	2.4 (10.89)
Weight percent change (%)				
N	106	223	118	63
Mean baseline (SD)	72.9 (17.87)	71.3 (13.22)	90.7 (23.27)	94.1 (24.35)
Mean change (SD)	0.2 (5.08)	2.2 (6.54)	2.5 (6.98)	3.2 (11.36)
Body mass index (kg/m2)				
N	106	223	118	63
Mean baseline (SD)	25.4 (5.13)	25.4 (4.48)	29.9 (7.45)	32.2 (8.81)
Mean change (SD)	0.0 (1.30)	0.5 (1.64)	0.7 (1.99)	0.8 (3.74)

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	Region: Rest of World		Region: Western Europe	
	Total Pali <=6 months (N=57)	Total Pali >6 months (N=95)	Total Pali <=6 months (N=52)	Total Pali >6 Months (N=99)
Weight (kg)				
N	45	32	42	40
Mean baseline (SD)	59.2 (12.69)	57.9 (12.27)	74.0 (19.28)	73.4 (16.27)
Mean change (SD)	1.5 (3.12)	3.6 (5.55)	1.1 (4.72)	1.3 (4.14)
Weight percent change (%)				
N	45	32	42	40
Mean baseline (SD)	59.2 (12.69)	57.9 (12.27)	74.0 (19.28)	73.4 (16.27)
Mean change (SD)	3.0 (5.70)	7.0 (10.57)	1.8 (7.45)	1.8 (5.38)
Body mass index (kg/m2)				
N	45	32	42	39
Mean baseline (SD)	22.1 (4.30)	21.7 (4.45)	26.0 (6.14)	26.2 (5.65)
Mean change (SD)	0.6 (1.14)	1.4 (2.24)	0.4 (1.75)	0.3 (1.44)

Baseline is double-blind baseline.
tsfvs08a_t1.rtf generated by tsfvs08a.sas.

Table 79: Number of Subjects With Abnormal Weight Values at End Point
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 Months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Weight classification	73	64	158	240	80	54	311	358
Decrease >= 7%	4 (5)	5 (8)	5 (3)	18 (8)	4 (5)	1 (2)	13 (4)	24 (7)
Increase >= 7%	8 (11)	8 (13)	25 (16)	49 (20)	15 (19)	19 (35)	48 (15)	76 (21)
Weight classification (OL)	74	64	158	240	80	54	312	358
Decrease >= 7%	3 (4)	5 (8)	1 (1)	14 (6)	5 (6)	4 (7)	9 (3)	23 (6)
Increase >= 7%	6 (8)	8 (13)	11 (7)	31 (13)	3 (4)	8 (15)	20 (6)	47 (13)

Note: Percentages calculated with the number of subjects per parameter as denominator.
Weight classification: relative to baseline(DB)
Weight classification (OL): relative to base(OPEN)
tsfvs10_t1.rtf generated by tsfvs10.sas.

7.2.9.2 210-Day Safety Update Report

The following table (provided in the 210-Day Safety Update Report dated 6/15/06) shows updated information on duration of Pal exposure in subjects in the ongoing integrated OL trial dataset.

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Table 12: Total Duration of Paliperidone Exposure – Double-Blind + Open-Label – Through 1 February 2006
(Studies R076477-SCH-702, 703, 704, and 705: Safety Analysis Set)

	— Pla/Pali — (N=236)	— Pali/Pali — (N=686)	— Olan/Pali — (N=249)	— Total — (N=1171)
Total duration of study medication (day)				
N	236	686	249	1171
Category, n (%)				
Week 1-4	35 (15)	4 (1)	44 (18)	83 (7)
Week 5-8	17 (7)	41 (6)	18 (7)	76 (6)
Week 9-12	17 (7)	58 (8)	16 (6)	91 (8)
Week 13-16	5 (2)	48 (7)	13 (5)	66 (6)
Week 17-20	5 (2)	36 (5)	6 (2)	47 (4)
Week 21-24	20 (8)	22 (3)	11 (4)	53 (5)
Week 25-28	18 (8)	14 (2)	11 (4)	43 (4)
Week 29-32	4 (2)	70 (10)	5 (2)	79 (7)
Week 33-36	5 (2)	13 (2)	3 (1)	21 (2)
Week 37-40	9 (4)	17 (2)	12 (5)	38 (3)
Week 41-44	18 (8)	27 (4)	15 (6)	60 (5)
Week 45-48	4 (2)	46 (7)	9 (4)	59 (5)
Week 49-52	43 (18)	34 (5)	53 (21)	130 (11)
> week 52	36 (15)	256 (37)	33 (13)	325 (28)
Mean (SD)	211.5 (136.79)	264.8 (134.87)	207.8 (144.02)	241.9 (139.80)
Median	202.0	302.0	238.0	272.0
Range	(1;391)	(26;437)	(2;392)	(1;437)

tsub18_t1.rtf generated by tsub18.sas.

Reviewer Comment. *Only a small number of additional subjects were exposed to over 6 moths of Pal treatment in the more recent 210-Day report (dated 6/15/06) compared to the number of subjects that received this longer term duration of treatment previous 120-Day SUR (see the table below copied form the 120-Day SUR). Given that the sample sizes between the 2 SURs are similar with only a few more additional subjects in the more recent report, a review of the 210-Day report was not conducted at this time for the purpose of this review. Furthermore, this SUR was provided late in the review cycle but is information that can be reviewed if the Agency grants an Approvable action on this NDA.*

Table 12: Total Duration of Paliperidone Exposure – Double-Blind + Open-Label – Through 1 November 2005
(Studies R076477-SCH-702, 703, 704, and 705: Safety Analysis Set)

	— Pla/Pali — (N=236)	— Pali/Pali — (N=685)	— Olza/Pali — (N=249)	— Total — (N=1170)
Total duration of study medication (day)				
N	236	685	249	1170
Category, n (%)				
Week 1-4	35 (15)	4 (1)	44 (18)	83 (7)
Week 5-8	17 (7)	41 (6)	18 (7)	76 (6)
Week 9-12	17 (7)	58 (8)	16 (6)	91 (8)
Week 13-16	5 (2)	48 (7)	13 (5)	66 (6)
Week 17-20	5 (2)	36 (5)	6 (2)	47 (4)
Week 21-24	20 (8)	22 (3)	11 (4)	53 (5)
Week 25-28	30 (13)	14 (2)	23 (9)	67 (6)
Week 29-32	13 (6)	99 (14)	13 (5)	125 (11)
Week 33-36	7 (3)	45 (7)	9 (4)	61 (5)
Week 37-40	4 (2)	31 (5)	7 (3)	42 (4)
Week 41-44	19 (8)	23 (3)	24 (10)	66 (6)
Week 45-48	9 (4)	27 (4)	15 (6)	51 (4)
Week 49-52	36 (15)	44 (6)	34 (14)	114 (10)
> week 52	19 (8)	193 (28)	16 (6)	228 (19)
Mean (SD)	195.4 (126.82)	247.0 (126.33)	188.8 (131.15)	224.2 (130.23)
Median	183.0	237.0	169.0	218.0
Range	(1;391)	(26;453)	(2;379)	(1;453)

dur48_tlf.sf generated by tssb13.sas

Deaths. No new deaths were reported in the 210-Day SUR.

SAEs in the Integrated OL Safety Dataset. A comparison by the undersigned reviewer of the summary table below enumerating SAEs as of the new 2/1/06 cut-off date to the 120-Day SUR table (shown previously in this review) on each of the following selected SAE terms revealed no new SAEs for these terms: cardiac disorder SAEs, completed suicide, suicide attempt, convulsion, grand mal convulsion, transient ischemic attack, investigations SAEs. Syncope was not reported as an SAE in any subject. 1 new subject had an SAE of suicide attempt (in the DB Placebo/OL Pal > 6 month subgroup) as of the more recent 2/1/06 cut-off date that does not appear on the sponsor's summary table in the 120-Day SUR. This additional subject does not alter the overall incidence in this subgroup (1%).

The sponsor provides a list of 46 new subjects with SAEs, ADOs and/or with AST or ALT of over 3 times the ULN that were not reported in the 120-Day SUR since they occurred between the 11/1/05 cut-off date for the 120-Day SUR and the 2/1/06 cut-off date for the 210-Day SUR.

These new subjects and other section of the 210-Day SUR have not yet been reviewed since this submission was received late in the review cycle (see Section 4.3 regarding the review strategy).

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This topic was addressed under each appropriate section.

7.4 General Methodology

See previous sections regarding concerns on methodology.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

See Section 7.1 where this topic is discussed.

Reviewer Comment. *See sections below. See Section 7.1 for pooled safety dataset methods. Specific limitations to safety datasets are discussed in detail in appropriate sections of this review that describe the results and the interpretation of results.*

7.4.1.2 Combining data

This topic is addressed above.

7.4.2 Explorations for Predictive Factors

See the following subsections. Also refer to Section 6 for subgroup analyses of efficacy data on the basis of age, gender and ethnic origin.

7.4.2.1 Explorations for dose dependency for adverse findings

Refer to the summary table of AEs in Section 7.1.5 showing the incidence of AEs for each Preferred Term for each treatment group. The incidence of several AEs appeared to be dose-dependent, as shown in summary tables provided in this review. Dose-dependent effects on other clinical parameters were also previously addressed in sections on each respective clinical parameter. Refer to the last section of this review for recommendations.

7.4.2.2 Explorations for time dependency for adverse findings

Examination safety parameters obtained at multiple time points were previously described and results were previously discussed in subsections of 7.1.

7.4.2.3 Explorations for drug-demographic interactions

Reviewer comments on results described below. *The results of only the placebo controlled, completed, short-term Phase III dataset analyses are described since these trials are completed, involved patients with schizophrenia and the trials were placebo controlled. The elderly Phase III trial, Study -302 had an insufficient sample size with the age-range skewed to over 65 year olds and within a rather narrow age-range. Consequently, results of an analyses on the basis of demographic subgroupings are considered difficult to interpret.*

Results of a Subgroup Analysis of Safety Parameters on the Basis of Origin Results on the basis of origin are difficult to interpret due to insufficient sample size of non-Caucasians. The sponsor analyses the incidence of AEs of each treatment group for the Short-term Phase III trial dataset (-303, -304 and -305) of "black" and "white" subgroups, since the number of subjects in other racial or ethnic groups were small. The incidence of AEs was numerically greater in the "black" subgroup compared to the "white" subgroups in each treatment group (75% and 65%, respectively in the placebo group, 75% and 70%, respectively in the Pal group and 70% and 67%, respectively in the olanzapine group).

Reviewer Comment. *These results suggest an absence of a drug by racial subgroup (between "black" and "white" subgroupings) interaction effect on the incidence of AEs. However, results are only considered preliminary since it is not clear if the results are reproduceable.*

Results of a Subgroup Analyses of Safety Parameters on the Basis of Age.
The sponsor subdivided subjects in each treatment group of the short-term Phase III trial dataset into 4 age-groups: 18-25 year olds, 26-50 year olds, 51-65 year olds and over 65 year olds. The sponsor selected these age-groups as an attempt to differentiate early onset schizophrenia (in the youngest age-group) from late onset and chronic schizophrenia (over 50 year olds). See reviewer comments below. The oldest age-group only had 10 subjects, therefore the sponor provided results for only the 3 younger age groups. See reviewer comments below which discuss the results and relevant issues.

Reviewer Comment. *It is speculative that the older age-groups represents a late-onset subgroup of patients, since a subgroup of these patients may have had an onset in early adulthood years. The incidence of AEs for the 3 youngest age-groups only differed by approximately 3-5% within each treatment group. These differences are not considered by the undersigned as clinically remarkable, particularly since it is know if findings are reproduceable.*

Results of a Subgroup Analyses of Safety Parameters on the Basis of Gender The following outlines the results on the incidence of AEs in males and females, respectively, in each treatment subgroup of the Phase III short-term trial dataset:

- Placebo subjects: 71% and 56%, respectively
- Olanzapine (72% and 64%)
- Paliperidone (68% and 77%)

Reviewer comment. *The results are difficult to interpret and to ascertain the clinical significance on the basis of overall incidence of AEs. However, the sponsor notes that the most frequently reported AEs in women compared to men who were assigned to DB Pal treatment in the Phase III trial dataset were the following: nervous system AEs, including extrapyramidal system AEs, gastrointestinal AEs and tachycardia (and sinus tachycardia).*

7.4.2.4 Explorations for drug-disease interactions

Explorations of potential drug-disease interactions could not be found in the SCS.

Reviewer's Comments. *As for most explorations in this section of the review, trials were not designed specifically to examine effects of each factor discussed in this section of the review, including the potential role of concomitant disorders. It is likely that concomitant disorders, as well as specific concomitant medications have significant effects on specific organ system effects, such as cardiovascular drug effects. Phase III trials included subjects with a past history of various medical disorders, however subjects had to be generally medically stable and meet specific eligibility criteria regarding their medical status and baseline clinical assessments.*

Drug class labeling for approved drugs generally has a section to address potential drug-disease interactions. Refer to the final section of this review for recommendations.

7.4.2.5 Explorations for drug-drug interactions

Potential drug-drug interactions on the safety profile of Pal were not systematically examined, as described in section 6.3.

Reviewer's Comments. *Drug class labeling for approved drugs generally has a section to address potential drug-disease interactions. Refer to the final section of this review for recommendations.*

7.4.3 Causality Determination

The above results of exploratory analyses are only preliminary observations such that causality cannot be inferred. Safety results of other sections and the potential role of Pal are previously discussed in this review.

8 ADDITIONAL CLINICAL ISSUES

See the final section of this review for any clinical issues that are recommended as issues that need to be address.

8.1 Dosing Regimen and Administration

See the final section of this review regarding the proposed treatment and any issues.

8.2 Drug-Drug Interactions

See the previous section 7.4.2.5 which covers this topic and the final section of this review for comments and recommendations relevant to this topic.

8.3 Special Populations

A Phase III study in elderly patients was conducted (Study -302) and efficacy and safety results on this study were previously described in Sections 6 and 7, respectively, in this review.

See the final section of this review for additional comment and recommendations relevant to this topic.

8.4 Pediatrics

The sponsor refers to meeting minutes of a 4/25/03 End-of-Phase II meeting in which the sponsor states the Division granted a waiver from performing studies patients ≤12 years old and a deferral for studies of 13-17 year old patients until their adult Phase III program is completed, as described in the section of the NDA submission entitled "Pediatric Use Information."

Reviewer comment and conclusion: *A pediatric waiver for the younger age-group is appropriate for the schizophrenia indication since schizophrenia is a disorder of the adult population with an age of onset that is generally in the young adult or adolescent (as considered by the majority of the clinical community and in accordance with the DSM-IV R). Furthermore, childhood psychotic-related disorders, as indicated in the DSM-IV R do not include Schizophrenia. A deferral for the adolescent population is reasonable and appropriate since Paliperidone is not currently approved for schizophrenia.*

8.5 Advisory Committee Meeting

An Advisory Committee (AC) meeting is to be held in September of 2006 on this NDA.

Reviewer Comment. *Given that risperidone is already on the market together with safety related concerns (e.g. QT prolongation) together with significant food effects and the need to establish a maximal (not-to-exceed dose-level) AD input is recommended. Not only do these issues exist but also relative to the benefit: risk ratio and as it compares to Risperdol.® The advantages of having Pal available to those of risperidone are not clear and do not appear to be clearly addressed in the submission. Moreover the advantages need to weighed against the risk relative to risperidone.*

8.6 Literature Review

Refer to Section 7.1.18. No new or remarkable information was revealed in the sponsor's search and review.

8.7 Postmarketing Risk Management Plan

A postmarketing risk plan cannot be found in the submission. Although, the sponsor maintains a postmarketing surveillance program for their approved formulations and is required by CRF codes to submit postmarketing reports (according the regulations).

8.8 Other Relevant Materials

This was already discussed.

9 OVERALL ASSESSMENT

This section reflects the opinions of the undersigned reviewer and from a clinical perspective, unless otherwise specified.

9.1 Conclusions

Pivotal Phase III trials were positive for establishing adequate efficacy, pending confirmation by the Office of Biometrics. The recommended dose in proposed labeling is also reasonable from an efficacy standpoint. However, there are several key issues that primarily pertain to establishing an adequately safe, yet efficacious dose range of Pal. Extensive experience with the already marketed Risperdol® provides some support in favor of the adequate safety of Pal. Yet, some key issues specific to Pal need to be resolved, such as a food effect on plasma levels, QT prolongation effects observed in Phase III trials and in a QT Prolongation study, among other safety findings that were not revealed in the Phase III trials of risperidone that supported approval for Risperdal® (as described in labeling).

Input from the Office of Clinical Pharmacology and Biopharmacy (OCPB) is critical in determining an adequately safe dose and treatment regimen and regarding other related issues (as outlined in the next subsection). Ultimately the risk: benefit ratio relative to the already available risperidone needs to be addressed. An Advisory Committee will be held in September of 2006.

A synopsis of key safety findings is provided under Section 7 of this review.

See key issues and recommendations in the next section below.

9.2 Recommendation on Regulatory Action

It is recommended that this NDA, be given an approvable action, from a clinical perspective.

The basis of this recommendation is discussed in the previous section and as follows. Although key issues remain unresolved that are relevant to safety, the dose-range found to be efficacious is sufficiently wide that given issues are resolved (as outline below), it is likely that an adequately

safe treatment regimen can be identified (with input from primarily OCPB given the food effect, QT prolongation effects and other safety signals). For example the 3 and 6 mg dose-levels appear to show adequate safety in clinical trials (as long the food effect is not an issue from a PK-safety perspective and given that labeling includes adequate information as recommended below). The critical issue is in identifying a maximum end of the dose-range for adequately safe treatment which remains unclear given the safety issues (the sponsor is proposing 3 to 12 mg under Dosage and Administration for labeling). OCPB input is critical for reasons specified below.

If an approvable action is granted at the Agency level on this NDA, then recommendations are provided below starting with a recommendation that impact on both safety and efficacy, followed by safety specific recommendations and efficacy-related recommendations follow, thereafter.

Recommendations that impact on both safety and efficacy:

1. The recommended starting dose and dose-range appears to be reasonable from an efficacy perspective but there are safety issues that also impact on dose, as described below. Therefore, these safety issues need to be addressed, as well before a recommended dose range can be made.
2. It is not clear if the [redacted] formulation was used in all pivotal efficacy trials (this question was conveyed to the sponsor and a response is pending at the time of this writing). OCPB input may be needed if a different formulation was used.

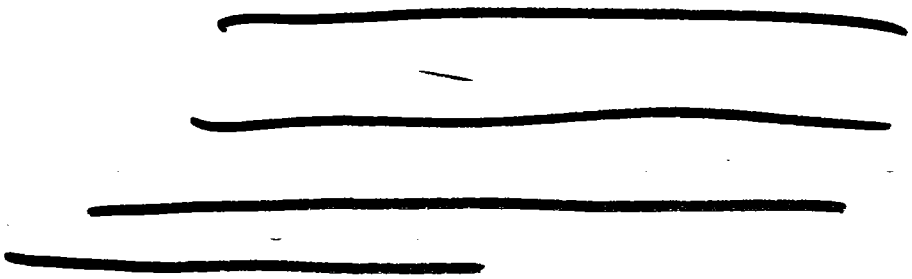
Safety Related Recommendations

If an approvable action is granted at the Agency level on this NDA, then the following outline contains comments and recommendations regarding safety (refer to Sections 7 and 9 of this review for an outline of safety findings, including those that are the basis of issues below):

1. A food effect on the pharmacokinetic (PK) properties of Pal was observed in two Phase I trials, as described in Section 5 of this review. This issue needs to be resolved with respect to recommendations for an adequately safe, yet efficacious treatment regimen. OCPB input is critical and recommended.
2. Food effects on PK and safety (in Phase I food effect studies described in Sections 5 for PK effects, 7.1.12 C and Section 7.1.3.3 for safety findings)
3. Several cardiovascular-related findings need to be addressed from a dose-level perspective that include a signal for
    - QT prolongation (based on Phase III data, updated longterm OL extension trial data provided in the 120-Day SUR, results of Study –SCH-1009),
    - Results on heart rate (based on ECG and vital sign results), and other hemodynamic effects were observed (based on results in Section 7). Subjects with clinically remarkable events related to hemodynamic Pal effects are also described in Section 7.1.3.3 of this review.
    - Potential PR interval prolongation effects as suggested by the following observations:

- A greater incidence of adverse events (AEs) of ° AV block in the 15 mg (highest-dose) Pal group compared to placebo (4.4%, 1.4%, respectively)
- Similar findings in the small elderly Phase III trial (3% and 0% in the Pal and placebo groups, respectively) that used a flexible dose design (3-12 mg/day),
- A small group mean increase in PR interval in Pal compared to placebo groups in Phase III trials (the magnitude of this increase was clinically unremarkable).

4. I



5. OCPB input is recommended regarding dosing recommendations in light of QT prolongation and other adverse effects and the potential PK-pharmacodynamic (PD) interactions (as well as other factors impacting PK such as a food effect, drug-drug interactions and others). Effects on QT and vital sign appear to be influenced by Cmax and Tmax (e.g. not only absolute levels but also perhaps how quickly levels are rising) and by other confounding variables (due to observations of direct or indirect time-dependent effects observed in Phase III trials and in Study –SCH-1009).
6. A more gradual dose adjustment (with a lower starting dose and longer interval between dose increments) and a lower maximum dose-level (not-to-exceed level) should be recommended for elderly patients and any other special populations, pending input from OCPB. It is noted that Risperdal® labeling provides specifications on dose adjustment in this section of labeling, although the recommendation is not specific to a given dose-level or maximum dose-level. This recommendation is being made on the basis of the following:
    - Safety findings in the elderly trial (-302), as outline in Sections1.1, 7 and 9 of this review,
    - Multiple concomitant medications and diseases are common in the elderly
    - The elderly are generally considered to have greater vulnerability to adverse effects (e.g. cardiovascular, ECG, CNS and other effects)
    - The elderly are more predisposed to alterations in PK (towards greater plasma levels),
    - There is the additional concern of a food effect on PK
    - A safety signal was revealed for increased risk of mortality in elderly patients with dementia being treated with atypical antipsychotics in longterm clinical drug trials (as described in drug class labeling of approved atypical antipsychotic agents). The role of age in this signal remains unclear.
7. Elevations in CPK levels were observed in treatment groups in Phase III trials. However, these elevations were inconsistent across treatment groups and may be reflective of the patient population rather than being drug-related. Yet, CPK levels varied widely across

subjects and showed large fluctuations over time within a given subject. Furthermore, baseline levels were elevated in some subjects and in some treatment groups. Consequently, it is difficult to detect a potential drug signal in a population with highly variable CPK levels at baseline. CPK elevations were also observed in Phase I trials of generally healthy subjects (who did not have schizophrenia) that appeared to be dose-dependent in subjects treated with the OROS formulation.

The sponsor does not describe any serious events associated with CPK elevations except for one subject (and possibly another with NMS that was found by the undersigned review; subjects 100057 and 200213). Additional subjects with elevated CPK were however, found by the undersigned reviewer that also had elevations in LFTs (as described in Section 7.1.3.3 of this review). There may be additional subjects with clinically remarkable events associated with CPK elevations since results of a special data analyses for revealing a potential drug-related signal could not be found in the Summary of Clinical Safety (SCS) section of the submission which provided the integrated summary of safety in clinical drug trials. Therefore, it is not clear to the undersigned if CPK elevations were associated with dystonia or other drug-related adverse effects. Another consideration is that CPK elevations reflective of the patient population would be expected to occur primarily in the acutely psychotic patient, yet elevations were also revealed during longterm OL Pal treatment (in the Phase III OL extension trials). This potential safety signal should be adequately resolved.

8. It is recommended that the specific methodology for dose adjustments during the OL trials (-702, -703, -704, and -705) be clarified (these trials used a flexible dose design). This information is relevant to longterm safety and may influence recommendations for dosage and administration in labeling.
9. Attachment 1 of this review lists questions raised to the sponsor to which some responses were received and other responses are pending at the time of this writing that should be resolved before considering a final approval action on this NDA (since some responses arrived late in the review cycle a review of these responses is pending, unless otherwise specified in this review).
10. Section 7.2.8 (on quality and completeness of data) discusses concerns related to identifying potentially clinically remarkable subjects with a specific type of AE (e.g. syncope, suicidality, among others). These issues should be adequately resolved. See Attachment 1 that includes some questions related to this concern (as described in the pervious item).
11. Once efficacy and safety related issues can be adequately addressed, then the sponsor would need to provide a convincing justification that the benefit: risk ratio of Pal outweighs that of Risperdol® (Ris).
12. Input from other disciplines is pending at the time of this writing.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The proposed Risk Management program cannot be found in the submission. In accordance with the Clinical Reviewer MAPP, a postmarketing studies and surveillance plan should be described here. Sponsors generally conduct ongoing postmarketing surveillance for safety signals and maintain a database. Sponsors of approved NDAs are also required to submit Periodic Safety Update reports according to regulations. If the Agency deems this NDA to be approvable consideration to obtaining input from the Office of Surveillance and Epidemiology is recommended.

9.3.2 Required Phase 4 Commitments

It is recommended that the sponsor address key issues as discussed in this review (as previously outlined and described in the final section of this review), before considering required Phase 4 commitments on this NDA.

The following are some considerations for studies that should enhance our understanding of cardiovascular effects of Pal:

- Conduct cardiovascular challenge tests (at baseline and during treatment) in double-blind, placebo controlled studies of patients with schizophrenia while monitoring vital signs and ECG (and in some cases with telemetry monitoring) using the following challenge paradigms for each given study:
    - Challenge subjects with a commonly used drug in the population that is known to have some degree of QT prolongation effects using adequately safe doses that would allow for detecting a signal while assuring adequate safety (e.g. the undersigned reviewer is the primary reviewer on the escitalopram NDA 21323 in which a pimozide-escitalopram interaction study revealed greater QT effects with this combination than with either of the two drugs alone.
    - Challenge subjects with a tread mill stress test (using methods for an adequately safe study).
    - Challenge subjects with a tilt table test
- Challenge subjects on longterm OL Pal (over 6 months to up to a year of treatment) with a higher daily dose of Pal (that is adequately safe) to determine if vital sign and QT effects can be elicited after a single dose and after subsequent multiple daily doses until at least steady state levels are achieved (subjects should undergo monitoring prior to starting the OL Pal treatment and throughout OL treatment to allow for pre-challenge and pre-Pal comparisons on cardiovascular parameters).
- Conduct a food challenge (food effect) study in patients with schizophrenia to examine the role of food effects on safety parameters (input from OCPB is recommended on this recommendation).
- Conduct studies to better characterize drug-drug and drug-disease interactions on cardiovascular effects and other relevant safety parameters.

- Other safety issues and PK issues may require further examination depending on the sponsor's responses to issues and on OCPB input.

There is the belief that antipsychotic drug treatment may be associated with or induce a metabolic syndrome (e.g. weight gain, abnormal lipid profile, hyperglycemia and other changes) that may increase risk for morbidity and possibly mortality in this population. Also consider a role of potential alterations in the endocrine system that may yet to be revealed or are known to exist (e.g. increased prolactin levels). Therefore, further study in this area should be considered.

Since elevations in LFTs were observed in some Pal subjects further study in this area should be considered such as employing a challenge test to determine if elevations can be elicited using methods that would be adequately safe. For example consider a study examine the effects of coadminstration of olanzapine (refer to labeling describing LFT elevations in some subjects on this drug). Polypharmacy involving multiple antipsychotic medications is not uncommon among clinicians treating patients with schizophrenia.

Phase III clinical trials using the OROS® formulation did not appear to test stools for bleeding and to monitor for excretion of capsules. A small group mean decrease in HgB was also observed that in itself is not clinically remarkable, yet could be reflecting a real drug-related effect (e.g. gastrointestinal bleeding perhaps due to retention of capsules). There was one subject with duodenal rupture and another subject with gastrointestinal hemorrhage reported in Phase III trials. It is recommended that consideration be given to studies focusing on a potential effect on OROS versus an effect of Pal on HgB and gastrointestinal bleeding, while also closely monitoring for signs and symptoms for GI complications, monitoring stools for occult blood and retention of capsules which were not systematically evaluated in Phase III trials.

9.3.3 Other Phase 4 Requests

See the previous section in which key issues first need to be addressed that can impact on the nature of Phase 4 requests.

9.4 Labeling Review

If an approvable action is granted at the Agency level on this NDA, then the following paragraphs are comments and recommendations regarding labeling.

3 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 4

Preclinical Team. It is common clinical practice to treat patients for years, given the chronicity of this disorder.

Karen Brugge, M.D.
Medical Reviewer,
FDA CDER ODE1 DPP HFD 130

cc: IND; HFD 130/N Khin/K Brugge/K Kiedrow/T Laughren/

APPENDIX

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Table Series 10.1 Schedule of Events of Phase III Trials (as provided by the sponsor)

Table 3: Time and Events Schedule
(Protocol R076477-SCH-303)

		Screening	Baseline	Double-Blind Treatment Phase								Post-Study Visit
	Visit	1	2	3	4	5	6	7	8	9	10	11
	Week	-1				1	2	3	4	5	6	7
Procedures	Day			1	4	8	15	22	29	36	43	50
Screening												
Inclusion/exclusion criteria		X	X									
Medical history		X										
Psychiatric evaluation		X										
Height		X										
Hemoglobin A_{1c}			X									
Oral glucose tolerance test		X										
Efficacy												
Positive and Negative Syndrome Scale (PANSS)		X	X		X	X	X	X	X	X	X	
Personal and Social Performance Scale (PSP)			X								X	
Clinical Global Impression Scale – Severity (CGI-S)			X		X	X	X	X	X	X	X	
Symptoms and Quality of Life in Schizophrenia Scale (SQLS)			X			X	X		X		X	
Sleep Visual Analog Scale (VAS)			X			X	X		X		X	
Safety												
Abnormal Involuntary Movement Scale (AIMS)			X			X	X	X	X	X	X	
Barnes Akathisia Rating Scale (BARS)			X			X	X	X	X	X	X	
Simpson Angus Scale (SAS)			X			X	X	X	X	X	X	
Clinical laboratory tests (fasting)[a]		X	X				X			X[b]	X	X
Vital signs		X	X	X[c]	X[c]	X	X	X	X	X	X	X
Electrocardiogram (ECG)		X[d]	X[d]		X[e]	X[e]	X[f]		X	X[f]	X	X
Physical examination, body weight, temperature		X									X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review			X	X	X	X	X	X	X	X	X	X
Pharmacokinetic blood sample[g]							X			X	X[h]	
Pharmacogenomic blood sample[i]			X									
Pregnancy test in females[j]		X									X	X
Administrative												
Informed consent		X										
Pharmacogenomic informed consent			X									
Hospitalization			X	X	X	X	X					
Randomization to treatment group[k]			X									
Dispense study drug				X	X	X	X	X	X	X		
Study drug accountability					X	X	X	X	X	X	X	

[a] Hematology, serum chemistry, and urinalysis. Laboratory samples were drawn in the fasting state.
[b] Prolactin levels only.
[c] Vital sign measurements were also obtained on Days 2, 3, 5, and 6.
[d] Three ECGs were recorded pretreatment, 2 recordings during screening (Days –5 to –1) and 1 recording at baseline.
[e] On Days 4 and 8, ECG recordings were obtained at 4, 10, and 22 hours after dosing.
[f] On Days 15 and 36, ECGs were recorded before blood samples were obtained for pharmacokinetic assessments (immediately predose, 1 to 2 hours after dosing, and 4 hours after dosing).
[g] Samples were obtained predose, 1 to 2 hours after dosing, and at least 4 hours after dosing.
[h] Sample was obtained only if a subject was withdrawn from the study before Visit 9.
[i] If blood sample was not collected at baseline (Visit 2), sample was collected at any time before Visit 10.
[j] Serum pregnancy test at screening (Visit 1) and post-study visit (Visit 11); urine pregnancy test at end of double-blind treatment phase (Visit 10).
[k] Contacted IVRS at baseline for randomization assignment.

Table Series 10.1, continued. Schedule of Events of Phase III Trials (as provided by the sponsor), continued.

Table 3: Time and Events Schedule
(Protocol R076477-SCH-304)

		Screening	Baseline	Double-Blind Treatment Phase								Post-Study Visit
	Visit	1	2	3	4	5	6	7	8	9	10	11
	Week	-1				1	2	3	4	5	6	7
Procedures	Day			1	4	8	15	22	29	36	43	50
Screening												
Inclusion/exclusion criteria		X	X									
Medical history		X										
Psychiatric evaluation		X										
Height		X										
Hemoglobin A_{1c}			X									
Oral glucose tolerance test		X										
Efficacy												
Positive and Negative Syndrome Scale (PANSS)		X	X		X	X	X	X	X	X	X	
Personal and Social Performance Scale (PSP)			X								X	
Clinical Global Impression Scale – Severity (CGI-S)			X		X	X	X	X	X	X	X	
Symptoms and Quality of Life in Schizophrenia Scale (SQLS)			X			X	X		X		X	
Sleep Visual Analog Scale (VAS)			X			X	X		X		X	
Safety												
Abnormal Involuntary Movement Scale (AIMS)			X			X	X	X	X	X	X	
Barnes Akathisia Rating Scale (BARS)			X			X	X	X	X	X	X	
Simpson Angus Scale (SAS)			X			X	X	X	X	X	X	
Clinical laboratory tests (fasting)[a]		X	X				X			X[b]	X	X
Vital signs		X	X	X[c]	X[c]	X	X	X	X	X	X	X
Electrocardiogram (ECG)		X[d]	X[d]		X[e]	X[e]	X[f]		X	X[f]	X	X
Physical examination, body weight, temperature		X									X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review			X	X	X	X	X	X	X	X	X	X
Pharmacokinetic blood sample[g]							X			X	X[h]	
Pharmacogenomic blood sample[i]			X									
Pregnancy test in females[j]		X									X	X
Administrative												
Informed consent		X										
Pharmacogenomic informed consent			X									
Hospitalization			X	X	X	X	X					
Randomization to treatment group[k]			X									
Dispense study drug				X		X	X	X	X	X		
Study drug accountability					X	X	X	X	X	X	X	

[a] Hematology, serum chemistry, and urinalysis. Laboratory samples were drawn in the fasting state.
[b] Prolactin levels only.
[c] Vital sign measurements were also obtained on Days 2, 3, 5, and 6.
[d] Three ECGs were recorded pretreatment, 2 recordings during screening (Days –5 to –1) and 1 recording at baseline.
[e] On Days 4 and 8, ECG recordings were obtained at 4, 10, and 22 hours after dosing.
[f] On Days 15 and 36, ECGs were recorded before blood samples were obtained for pharmacokinetic assessments (immediately predose, 1 to 2 hours after dosing, and 4 hours after dosing).
[g] Samples were obtained predose, 1 to 2 hours after dosing, and at least 4 hours after dosing.
[h] Sample was obtained only if a subject was withdrawn from the study before Visit 9.
[i] If blood sample was not collected at baseline (Visit 2), sample was collected at any time before Visit 10.
[j] Serum pregnancy test at screening (Visit 1) and post-study visit (Visit 11); urine pregnancy test at end of double-blind treatment phase (Visit 10).
[k] Contacted IVRS at baseline for randomization assignment.

Table Series 10.1, continued. Schedule of Events of Phase III Trials (as provided by the sponsor), continued.

Table 3: Time and Events Schedule
(Protocol R076477-SCH-302)

	Screening	Baseline	Double-Blind Treatment Phase								Post-Study Visit
Visit	1	2	3	4	5	6	7	8	9	10	11
Week	-1				1	2	3	4	5	6	7
Procedures / Day			1	4	8	15	22	29	36	43	50
Screening											
Inclusion/exclusion criteria	X	X									
Medical history	X										
Psychiatric evaluation	X										
Height	X										
Hemoglobin A_{1c} (HbA_{1c})		X									
Oral glucose tolerance test	X										
Efficacy											
Positive and Negative Syndrome Scale (PANSS)	X	X		X	X	X	X	X	X	X	
Personal and Social Performance Scale (PSP)		X								X	
Clinical Global Impression Scale – Severity (CGI-S)		X		X	X	X	X	X	X	X	
Schizophrenia Quality of Life Scale (SQLS)		X			X	X		X		X	
Sleep Visual Analog Scale (VAS)		X			X	X		X		X	
Safety											
Abnormal Involuntary Movement Scale (AIMS)		X		X	X	X	X	X	X	X	
Barnes Akathisia Rating Scale (BARS)		X		X	X	X	X	X	X	X	
Simpson Angus Scale (SAS)		X		X	X	X	X	X	X	X	
Clinical laboratory tests (fasting)[a]	X	X				X			X[b]	X	X
Vital signs	X	X	X[c]	X[c]	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X[d]	X[d]		X[e]	X[e]	X[f]		X	X[f]	X	X
Physical examination, body weight, temperature	X									X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X
Pharmacokinetic blood sample[g]						X			X	X[h]	
Pharmacogenomic blood sample[i]		X									
Administrative											
Informed consent	X										
Pharmacogenomic informed consent	X										
Hospitalization		X	X	X	X	X					
Randomization to treatment group[j]		X									
Dispense study drug			X	X	X	X	X	X	X		
Study drug accountability				X	X	X	X	X	X	X	

[a] Hematology, serum chemistry, and urinalysis. Laboratory samples were drawn in the fasting state.
[b] Prolactin levels only.
[c] Vital sign measurements were also obtained on Days 2, 3, 5, and 6.
[d] Three ECGs were recorded pretreatment, 2 recordings during screening (Days –5 to –1) and 1 recording at baseline.
[e] On Days 4 and 8, ECG recordings were obtained at 4, 10, and 22 hours after dosing.
[f] On Days 15 and 36, ECGs were recorded before blood samples were obtained for pharmacokinetic assessments (immediately predose, 1 to 2 hours after dosing, and 4 hours after dosing).
[g] Samples were obtained predose, 1 to 2 hours after dosing, and at least 4 hours after dosing.
[h] Sample was obtained only if a subject was withdrawn from the study before Visit 9.
[i] If blood sample was not collected at baseline (Visit 2), the sample was collected at any time before Visit 10.
[j] Contacted IVRS at baseline for randomization assignment.

Table Series 10.2 Outlier Criteria Employed for Clinical Parameters (as provided by the sponsor) for Completed Phase III Trials (-303, -304 and -305).

Criteria for Identification of Markedly Abnormal Clinical Laboratory Analyte Values

Study R076477-SCH-304

Output DLAB06: Criteria for Identification of Markedly Abnormal Clinical Laboratory Analyte Values

Laboratory Parameter	Clinically Significant Low in STD Unit	Clinically Significant High in STD Unit
SODIUM (mmol/l)	125	155
POTASSIUM (mmol/l)	3	5.8
CHLORIDE (mmol/l)	94	112
BICARBONATE (mmol/l)	15.1	34.9
GLUCOSE (mmol/l)	2.2204	16.653
AST (SGOT) (U/L)	N/A	250
ALT (SGPT) (U/L)	N/A	200
UREA NITROGEN (mmol/l)	N/A	17.85
CREATININE (umol/l)	N/A	265.2
LDL (mmol/l)	2.30154	4.1376
HDL (mmol/l)	0.9051	N/A
CHOLESTEROL (mmol/l)	N/A	7.758
TRIGLYCERIDES (mmol/l)	N/A	5.715
CREATINE KINASE (U/L)	N/A	990
WBC (giga/l)	2.5	15
RBC (tera/l)--FEMALE	3	5.5
RBC (tera/l)--MALE	3	6.4
HEMOGLOBIN (g/l)	80	190
HEMATOCRIT (l)--FEMALE	0.29	0.5
HEMATOCRIT (l)--MALE	0.24	0.55
PLATELETS (giga/l)	100	600
RETICULOCYTES (%)--FEMALE	0.9	4.4
RETICULOCYTES (%)--MALE	1	3.8
NEUTROPHILS (%)	30	90
LYMPHOCYTES (%)	10	60
MONOCYTES (%)	N/A	20
EOSINOPHILS (%)	N/A	10
BASOPHILS (%)	N/A	6
ALBUMIN (g/l)	24	60
ALKALINE PHOSPHATASE (U/L)	N/A	250
CALCIUM (mmol/l)	1.497	2.994
GGT (U/L)	N/A	300
LDH (U/L)	N/A	500
PHOSPHORUS (mmol/l)	0.71038	2.61549
BILIRUBIN (umol/l)	N/A	51.3
PROTEIN (g/l)	50	N/A
URIC ACID (umol/l)	89.22	594.8
HAEMOGLOBIN A1C (%)	4.3	6.1
DIRECT BILIRUBIN (umol/l)	N/A	6.84

Note: The same limits apply to both male and female unless gender is indicated
N/A=Not applicable

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Table Series 10.2, continued Outlier Criteria Employed for Clinical Parameters (as provided by the sponsor) for Study -302

Attachment 8.3.1: Criteria for Markedly Abnormal Laboratory Values

	Markedly Abnormal Limits	
Laboratory Test	Low	High
Albumin (g/dL)	2.4	6.0
Alkaline phosphatase (µ/L)	N/A	250
Alanine transaminase (SGPT) (µ/L)	N/A	200
Aspartate transaminase (SGOT) (µ/L)	N/A	250
Bicarbonate (mEq/L)	15.1	34.9
Blood urea nitrogen (mg/dL)	N/A	50
Calcium (mg/dL)	6	12
Chloride (mEq/L)	94	112
Cholesterol (mg/dL)	N/A	300
Creatine kinase (µ/L)	N/A	990
Creatinine (mg/dL)	N/A	3
Gamma glutamyl transferase (µ/L)	N/A	300
Glucose (mg/dL)	40	300
HDL (mg/dL)	30	N/A
LDH (µ/L)	N/A	500
LDL (mg/dL)	98	224
Phosphorus (mg/dL)	2.2	8.1
Potassium (mEq/L)	3.0	5.8
Sodium (mEq/L)	125	155
Total bilirubin (mg/dL)	N/A	3.0
Total protein (g/dL)	5	N/A
Triglycerides (mg/dL)	N/A	500
Uric acid (mg/dL)	1.5	10
Hematocrit (%)-- female	28	50
-- male	24	55
Hemoglobin (g/dL)	8	19
Neutrophils (%)	30	90
Monocytes (%)	N/A	20
Eosinophils (%)	N/A	10
Basophils (%)	N/A	6
Lymphocytes (%)	10	60
Platelet count ($x10^3/\mu L$)	100	600
Red blood cell count ($x10^6/\mu L$) -- female	3.0	5.5
-- male	3.0	6.4
Reticulocytes (%)-- female	0.9	4.4
-- male	1.0	3.8
White blood cell count ($x10^3/\mu L$)	2.5	15.0

Note: The same limits apply to both males and females unless gender is indicated;
N/A = Not applicable.

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Table Series 10.2, continued Outlier Criteria Employed for Clinical Parameters (as provided by the sponsor)

Table 75: Criteria for Treatment-Emergent Abnormal Vital Signs, Orthostatic Changes, and Body Mass Index

Parameter	Outside of normal limit if ... Abnormally low		Abnormally high
Vital signs:			
Pulse (bpm)	A decrease from baseline of ≥ 15 to a value ≤ 50		An increase from baseline of ≥ 15 to a value ≥ 100
Systolic blood pressure (mm Hg)	A decrease from baseline of ≥ 20 to a value ≤ 90		An increase from baseline of ≥ 30 to a value ≥ 180
Diastolic blood pressure (mm Hg)	A decrease from baseline of ≥ 15 to a value ≤ 50		An increase from baseline of ≥ 15 to a value ≥ 105
Body weight (kg)	A decrease from baseline of ≥ 7%		An increase from baseline of ≥ 7%
Orthostatic changes in:			
Systolic blood pressure (mm Hg)	>15		
Diastolic blood pressure (mm Hg)	< -30		
Pulse (bpm)	< -10		
	Normal	Overweight	Obese
Body mass index (BMI)	< 25	25 - <30	≥ 30

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Table 84: Criteria for Abnormal Electrocardiographic Findings

ECG parameter		Abnormally low	Abnormally high
HR (bpm)		≤ 50	≥ 100
PR interval (msec)		--	≥ 210
QRS interval (msec)		≤ 50	≥ 120
QT interval (msec)		≤ 200	≥ 500
QTc value (msec)	**Classification**	**Adult Males**	**Adult Females**
	Normal	≤ 430	≤ 450
	Borderline	431 – 450	451 – 470
	Prolonged	> 450	> 470
		Adult Males and Females	
Clinically significant value	No	< 500	
	Yes	≥ 500	
Change from baseline	No concern	< 30	
	Concern	30 – 60	
	Clear concern	> 60	
QTc Classification[a]	Normal	<450	
	≥450	≥450 and <480	
	≥480	≥480	

[a] Classification based on ICH E14 Guideline (reference 4).

Table 10.3 Study Schedule for Study SCH-1009

TIME AND EVENTS SCHEDULE

Study Procedure	Screening Period			Randomization Period: Treatment Phase						Randomization Period: Post-treatment Phase		End of Study/ Early Withdrawal
Day:	−14 to −3[a]	−2	−1	1	2	3	4	5 to 7	8	9	10	
Screening/Administrative Procedures												
Informed consent	X											
Inclusion/exclusion criteria	X											
Medical, psychiatric histories	X											
Psychiatric evaluation	X											
Physical examination	X											X
Body weight	X											
Height	X											
Prior medication	X											
Urine drug screening[b]	X	X										
Alcohol test		X										
Randomization to treatment group				X								
Hospitalization[c]		X	X	X	X	X	X	X	X	X	X	
Discharge from hospital											X	
Study Drug Administration[d]												
Administer oral study medication (paliperidone, moxifloxacin, or placebo)				X	X	X	X	X	X			
Study drug accountability				X	X	X	X	X	X			
Pharmacodynamic Procedures												
12-lead electrocardiogram[e]	X		X	X	X	X	X	X[a]	X	X	X	X[f]
Pharmacokinetic Procedures												
Documentation of meal time and content[g]			X	X	X	X	X	X	X	X	X	
Blood sample collection[e]				X	X	X	X	X[a]	X	X	X	
Pharmacogenomic Procedures												
Informed consent	X	(X)										
Blood sample collection				X								
Safety Procedures												
Vital signs[h]	X	X	X									X
Clinical laboratory tests	X	X										X
Pregnancy test in women[i]	X	X										X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X

NOTE: Footnotes are provided on the following page. (Continued)

Table 10.3 Study Schedule for Study SCH-1009, continued.

TIME AND EVENTS SCHEDULE (CONTINUED)

[a] All medications that subjects are currently taking at enrollment must be washed out. A minimum washout period of 5 days prior to study start will be adequate except in the case of certain medications (see Section 4.3).
[b] All subjects will be tested for drugs of abuse at both screening and Day –2. Subjects who test positive for drugs of abuse at screening must have a negative test when re-tested on Day –2 prior to randomization.
[c] Subjects may also be hospitalized during the washout period, based on the clinical judgment of the investigator.
[d] Study medication (paliperidone, moxifloxacin, and placebo) will all be identical in appearance, in order to preserve the blind.
[e] Specific times for dosing, electrocardiogram (ECG), and pharmacokinetic sampling are provided in Table 1 in Section 9.1.1. On Days 5, 6, and 7, pharmacokinetic blood sampling will only be predose; on Day 5, ECG recording will only be predose.
[f] A single ECG will be performed upon early withdrawal if no ECG has been performed that day.
[g] Caffeine/methylxanthine-containing beverages or foods (including chocolate) are not allowed within 2 hours prior to each ECG recording. High-fat- and high-sugar-containing foods must be minimized. Meals must be scheduled so that subjects will have at least 30 minutes of rest prior to an ECG recording, and conditions in the unit must be modified so that both physical and emotional stress are minimized prior to ECG recording.
[h] Supine blood pressure, pulse, and oral temperature.
[i] Serum test will be performed at screening and end of study/early withdrawal; urine test will be performed on Day –2.

Table 10.4 PK Blood Sampling and ECG Assessment Time-points for Study SCH-1009.

R076477 (paliperidone): Clinical Protocol R076477-SCH-1009

Table 1: Schedule for ECG Recordings and Pharmacokinetic Sampling

Study Day	Hour (Target)	Time Relative to Dosing (hours)[a]	Study Drug Administration	12-Lead ECG[b]	Pharmacokinetic Sampling[c]
Day –1	08:00	–24		X	
Days 1 and 2	08:00	0	X	X[d]	X[d]
	08:30	0.5		X	X
	09:00	1		X	X
	09:30	1.5		X	X
	10:00	2		X	X
	10:30	2.5		X	X
	11:00	3		X	X
	11:30	3.5		X	X
	12:00	4		X	X
	14:00	6		X	X
	20:00	12		X	X
Days 3 and 4	08:00	0	X	X[d]	X[d]
	08:30	0.5		X	
	09:00	1		X	X
	09:30	1.5		X	
	10:00	2		X	X
	10:30	2.5		X	
	11:00	3		X	
	11:30	3.5		X	
	12:00	4		X	X
	14:00	6		X	
	20:00	12		X	X
Day 5	08:00	0	X	X[d]	X[d]
Days 6 and 7	08:00	0	X		X[d]
Day 8	08:00	0	X	X[d]	X[d]
	08:30	0.5		X	X
	09:00	1		X	X
	09:30	1.5		X	X
	10:00	2		X	X
	10:30	2.5		X	X
	11:00	3		X	X
	11:30	3.5		X	X
	12:00	4		X	X
	14:00	6		X	X
	20:00	12		X	X
Day 9	08:00	24		X	X
	08:30	24.5		X	
	09:00	25		X	
	09:30	25.5		X	
	10:00	26		X	
	10:30	26.5		X	
	11:00	27		X	
	11:30	27.5		X	

(Continued)

Table 10.4 PK Blood Sampling and ECG Assessment Time-points for Study SCH-1009, continued.

Study Day	Hour (Target)	Time Relative to Dosing (hours)[a]	Study Drug Administration	12-Lead ECG[b]	Pharmacokinetic Sampling[c]
Day 9 (continued)	12:00	28		X	
	14:00	30		X	
	20:00	36		X	X
Day 10	08:00	48		X	X
	08:30	48.5		X	
	09:00	49		X	
	09:30	49.5		X	
	10:00	50		X	
	10:30	50.5		X	
	11:00	51		X	
	11:30	51.5		X	
	12:00	52		X	
	14:00	54		X	
	20:00	60		X	X

[a] Time on Day –1 is relative to the Day 1 dosing; time on Days 1 to 7 is relative to that day's dosing; time on Days 8, 9, and 10 is relative the Day 8 dosing.
[b] Triplicate 10-sec recordings collected at 60-sec intervals.
[c] Within 5 min after each triplicate ECG recording, where applicable.
[d] Predose.

Table 10.5 Visit Windows of Phase I-III Trials

Table Ia: Time Intervals for ECG, Lab, Vitals and EPS Scales Visits for R076477-SCH-303, 304, and 305

Variable	Scheduled Visit Number	Time Interval (Label on ouput)	Time Interval (Day)[a]	Target Time Point (Day)
ECG	1,2	Baseline	≤ 1	1
	4	Day 4: 4H pst-ds	2-6[b]	4
	4	Day 4: 10H pst-ds	2-6[b]	4
	4	Day 4: 22H pst-ds	2-6[b]	4
	5	Day 8: 4H pst-ds	7-11[b]	8
	5	Day 8: 10H pst-ds	7-11[b]	8
	5	Day 8: 22H pst-ds	7-11[b]	8
	6	Day 15: pre-ds	12-22	15
	6	Day 15: 1-2H pst-ds	12-22	15
	6	Day 15: 4H pst-ds	12-22	15
	8	Day 29	23-32	29
	9	Day 36: Pre-ds	33-39	36
	9	Day 36: 1-2H pst-ds	33-39	36
	9	Day 36: 4H pst-ds	33-39	36
	10	Day 43	40-end of DB	43
Labs	1,2	Baseline	≤1	1
	6	Day 15	2-29[c], 2-32[d]	15
	9	Day 36	33-39[d]	36
	10	Day 43	30-end of DB[c] 40-end of DB[d]	43
SAS/BARS/AIMS	1,2	Baseline	≤ 1	1
	5	Day 8	2-11	8
	6	Day 15	12-18	15
	7	Day 22	19-25	22
	8	Day 29	26-32	29
	9	Day 36	33-39	36
	10	Day 43	40-end of DB	43
Vital Signs	1,2	Baseline	≤ 1	1
	3	Day 2	2	2
	3	Day 3	3	3
	4	Day 4	4	4
	4	Day 5	5	5
	4	Day 6	6	6
	5	Day 8	7-11	8
	6	Day 15	12-18	15
	7	Day 22	19-25	22
	8	Day 29	26-32	29
	9	Day 36	33-39	36
	10	Day 43	40-end of DB	43

[a] Relative to the first day of double-blind study drug administration
[b] Time point will be assessed based on the scheduled elapsed time (EGPTMNUM) in the data set.
[c] Applicable to all laboratory tests except for prolactin.
[d] Only for prolactin that is assessed at Day 36.

Table 10.5 series, continued.

Table 1b: Time Intervals for ECGs and Lab Visits for R076477-SCH-302

Variable	Scheduled Visit Number	Time Interval (Label on ouput)	Time Interval (Day)[a]	Target Time Point (Day)
ECG	1,2	Baseline	≤ 1	1
	4	Day 4: 4H pst-ds	2-6[b]	4
	4	Day 4: 10H pst-ds	2-6[b]	4
	4	Day 4: 22H pst-ds	2-6[b]	4
	5	Day 8: 4H pst-ds	7-11[b]	8
	5	Day 8: 10H pst-ds	7-11[b]	8
	5	Day 8: 22H pst-ds	7-11[b]	8
	6	Day 15	12-22	15
	8	Day 29	23-35	29
	10	Day 43	36-end of DB	43
Labs	1,2	Baseline	≤1[c,d]	1
	6	Day 15	2-29[c], 2-32[d]	15
	9[f]	Day 36[d]	33-39[d]	15
	10	Day 43	30-end of DB[c], 40-end of DB[d]	43

[a] Relative to the first day of double-blind study drug administration
[b] Time point will be assessed based on the scheduled elapsed time (EGPTMNUM) in the data set.
[c] Applicable to all laboratory tests except for prolactin.
[d] Only for prolactin that is assessed also at Visit 9 (Day 36).

Table 10.5 series, continued.

Table 2a: Time Intervals for Double-Blind Data Summarized in Open-Label Studies

Analysis	Time interval label in R076477-SCH-304	Time interval label in R076477-SCH-704
Double-blind	Baseline	Baseline (DB)
	Day 1	Day 1 (DB)
	Day 1 LOCF	Day 1 (DB) LOCF
	Day 4	Day 4 (DB)
	Day 8	Day 8 (DB)
	Day 8 LOCF	Day 8 (DB) LOCF
	Day 15	Day 15 (DB)
	Day 15 LOCF	Day 15 (DB) LOCF
	Day 22	Day 22 (DB)
	Day 22 LOCF	Day 22 (DB) LOCF
	Day 29	Day 29 (DB)
	Day 29 LOCF	Day 29 (DB) LOCF
	Day 36	Day 36 (DB)
	Day 36 LOCF	Day 36 (DB) LOCF
	Day 43	Day 43 (DB)
	Day 43 LOCF	Day 43 (DB) LOCF
	End point	End point (DB)

Table 10.5 series, continued.

Table 2b: Time Intervals for Open-Label Studies

Variable	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
Vital Signs	Open-label	101	Base (open)	-14 to 1	1
		102	Day 4	2 to 6	4
		103	Week 1 (open)	7 to 11	8
		104	Week 2 (open)	12 to 18	15
		105	Week 3 (open)	19 to 25	22
		106	Week 4 (open)	26 to 43	29
		107	Week 8 (open)	44 to 71	57
		108	Week 12 (open)	72 to 99	85
		109	Week 16 (open)	100 to 127	113
		110	Week 20 (open)	128 to 155	141
		111	Week 24 (open)	156 to 183	169
		112	Week 28 (open)	184 to 211	197
		113	Week 32 (open)	212 to 239	225
		114	Week 36 (open)	240 to 267	253
		115	Week 40 (open)	268 to 295	281
		116	Week 44 (open)	296 to 323	309
		117	Week 48 (open)	324 to 351	337
		118	Week 52 (open)	352 to 370	365
		119	Week 53 (open)	>370	372
Labs	Open-label	101	Base (open)	-14 to 1	1
		111	Week 24 (open)	2 to 267	169
		118	Week 52 (open)	268 to 370	365
		119	Week 53 (open)	>370	372
ECG	Open-label	101	Base (open)	-14 to 1	1
		102	Day 4	2 to 6	4
		103	Week 1 (open)	7 to 11	8
		104	Week 2 (open)	12 to 18	15
		106	Week 4 (open)	19 to 43	29
		107	Week 8 (open)	44 to 85	57
		109	Week 16 (open)	86 to 141	113
		111	Week 24 (open)	142 to 225	169
		115	Week 40 (open)	226 to 337	281
		118	Week 52 (open)	338 to 370	365
		119	Week 53 (open)	>370	372

[a] Day 1 is the day of the first dose in open-label study.

Table 10.6 series. Phase I Dose Group Classifications for the Phase I Safety Dataset Selected by the Sponsor for Presenting Data Described in the Summary of Clinical Safety section of the Submission and is Summarized in Section 7 of this Review

To make the diverse Phase 1/2a treatments comparable, they were classified in 6 treatment groups as indicated in Tables 3 and 4. All results will be summarized by these groups, unless specified otherwise. The 6 treatment groups, in order of their appearance in all summaries, are:

a. Placebo: all placebo treatments.

b. Pali IR: all Immediate Release treatments, including IV injection, oral solutions with C14 label, (+) and (-) enantiomers, oral solutions and tablets with racematic mixtures.

c. Pali other: all experimental formulations with doses between 2 and 6 mg paliperidone, including the osmotic modules, the paliperidone flat and ascending profiles, the coated OROS in R076477-P01-101, the [redacted] OROS in ALZA C-2002-034 and all [redacted] formulations.

d. Pali OROS low dose: all 3 to 6 mg doses with OROS formulations, including 2 mg tablets ([redacted] OROS or Phase 1 formulation), and 3 and 6 mg ER OROS paliperidone.

e. Pali OROS high dose: all 9 to 15 mg doses using Phase 1 (2 mg tablets), Phase 3 [redacted] OROS formulations and a first day of placebo in a one week paliperidone group in the R076477-SCH-101 study, followed by 12 mg paliperidone OROS (as in the original clinical study report).

f. Risperidone: all 2 to 8 mg oral risperidone treatments, including risperidone ascending profiles, osmotic modules, oral solutions and IR tablets.

Table 10.6 series, continued. Dose Group Classifications for the Phase I Safety Dataset ..., continued.

Per summary, there will be 3 tables for the pooled phase 1/2a analyses, excluding overall totals, unless otherwise specified:

- Healthy young subjects, excluding ER OROS treatments, but including columns: (a), (b), (c), sum of (b) and (c), (f).
- Healthy young subjects receiving ER OROS paliperidone, with the columns: (d), (e), sum of (d) and (e).
- Subjects with schizophrenia with the columns: (b), (e) and (f).

Table 3: Pooled Phase 1 Studies in Healthy Young Subjects

Protocol Number	Study Treatment Label	SCS Treatment Group
Alza C-2001-032	RIS 2mg OSM MOD	risperidone
	RIS 2mg OS	risperidone
	PAL 2mg OSM MOD	pali other
	PAL 2mg OS	pali IR
Alza C-2001-039	PAL 5.5mg ASCEND (3.5 ASC+2IR)	pali other
	PAL 4.5mg FLAT (2.5 FLAT+2IR)	pali other
	PAL 4mg IR(2*2mg)	pali IR
	PLACEBO	placebo
Alza C-2002-019	RIS 6mg ASCEND (4mg ASC+2IR)	risperidone
	PAL 6mg ASC-4 (4mg ASC+2IR)	pali other
	PAL 4mg ASC-2 (2mg ASC +2IR)	pali other
	RIS 4mg IR-2 (2*2mg IR)	risperidone
	PLACEBO	placebo
Alza C-2002-034	PAL 4mg [redacted] OROS Fasted	pali other
	PAL 4mg [redacted] OROS Fasted	pali OROS low dose
	PAL 4mg [redacted] OROS Fed	pali OROS low dose
	PAL 2mg IR Fasted	pali IR low dose
Alza C-2003-044	PAL 6mg OROS	pali OROS low dose
	PAL 9mg OROS	pali OROS high dose
	PAL 12mg OROS	pali OROS high dose
	PAL 15mg OROS	pali OROS high dose
Alza C-2004-006	PAL 12mg OROS Fasted	pali OROS high dose
	PAL 15mg OROS Fasted	pali OROS high dose
	PAL 15mg OROS Fasted	pali OROS high dose
	PAL 15mg OROS Fed	pali OROS high dose
R076477-BEL-1	PAL 0.5mg OS Fasted	pali IR
	PAL 0.5mg TAB Fasted	pali IR
	PAL 0.5mg TAB Fed	pali IR
R076477-P01-101	PAL 2.5mg [redacted] Fasted	pali other
	PAL 2.5mg [redacted] Fed	pali other
	PAL 4mg coated OROS Fasted	pali other
	PAL 4mg coated OROS Fed	pali other
	PAL 2mg OS Fasted	pali IR
R076477-P01-102	PAL 2.5mg [redacted]-1 Fasted	pali other
	PAL 2.5mg [redacted]-1 Fed	pali other

Table 10.6 series, continued. Dose Group Classifications for the Phase I Safety Dataset ..., continued.

Protocol Number	Study Treatment Label	SCS Treatment Group
	PAL 2.5mg [redacted] -2 Fasted	pali other
	PAL 2.5mg [redacted] -2 Fed	pali other
	PAL 2mg OS Fasted	pali IR
R076477-P01-103	PAL 1mg C14 OS	pali IR
R076477-P01-1006	PAL 3mg OROS, Fasted in Jap.	Pali OROS low dose
	PAL 3mg OROS, Fed in Jap.	Pali OROS low dose
R076477-P01-1007	PAL 1mg OS	pali IR
	PAL 3mg OROS	pali OROS low dose
	PAL 1mg IV	pali IR
	PAL(+) 1mg OS	pali IR
	PAL(-) 1mg OS	pali IR
R076477-P01-1008	PAL 15mg OROS Phase 3, fasted	pali OROS high dose
	PAL 15mg OROS [redacted], fasted	pali OROS high dose
	PAL 15mg OROS [redacted] fed	pali OROS high dose
R076477-P01-1010	PAL 3mg OROS	pali OROS low dose
	PAL 6mg OROS	pali OROS low dose
	PAL 9mg OROS	pali OROS high dose
	PAL 12mg OROS	pali OROS high dose
	PAL 15mg OROS	pali OROS high dose
R076477-SIV-101	PAL 6mg OROS	pali OROS low dose
R076477-SWE-1	PAL 1mg	pali IR
RIS-BEL-28	RIS IR 1mg	risperidone
	PAL IR 1mg	pali IR
	PLACEBO	placebo

Table 4: Pooled Phase 1/2a Studies in Subjects with Schizophrenia

Protocol Number	Study Treatment Label	SCS Treatm. Group
R076477-INT-1	PAL 1mg TAB	pali IR
	PAL 2-4mg TAB	pali IR
	PAL 2-8mg TAB	pali IR
R076477-SCH-101	PLAC/PAL 12mg OROS	pali OROS high dose
	PAL 12mg OROS	pali OROS high dose
	RIS IR 2-4mg	risperidone
R076477-SCH-102	PAL 9-15mg OROS	pali OROS high dose
	RIS IR 1-8mg	risperidone

ATTACHMENTS

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Attachment 1. Questions to the Sponsor (refer to DFS).

Questions Conveyed to the Sponsor
(a response to Question 1 was e-mailed, pending submission under the NDA) and
Outstanding Questions
(responses to Question 2-4 are pending at the time of this writing)

-----Original Message-----
From: Brugge, Karen [mailto:karen.brugge@fda.hhs.gov]
Sent: Wednesday, June 28, 2006 10:46 AM
To: Martynowicz, Jadwiga [PRDUS]
Cc: sochalsk@prdus.jnj.com; Khin, Ni Aye; Kiedrow, Keith
Subject: RE: Outstanding SCH-1009 Qs & Miscellaneous

Hi Heddie,

Thanks for your responses and we look forward to your response to the syncope-related Q.

This e-mail is a follow-up to your last response regarding SCH-1009 (see Q1 below), 2 new questions that we were hoping you could help us with (see Q 2 and 3), and examples of dropouts that we said we would be sending you (Q 4). Q 5 below is related to our examples of dropouts but is regarding subject 100057 who had adverse events ("muscle stiffness over the entire body" and other AEs during treatment that were followed by a serious adverse event (SAE) of neuroleptic malignant syndrome within days of treatment cessation that was not captured in the SAE database. Thanks for your assistance on getting the answers to our questions.

1. We received the most recent response about Study -1009-related Qs (forwarded with this e-mail). Just to be sure we don't miss anything, it looks like there is only 1 outstanding Q on this study which is the following about gender (we recently discussed this outstanding Q with you and I then sent you a follow-up e-mail from which I've copied key sections below for your convenience).

The raw mean QT and QTc values (for each method except for Bazett's) of each treatment condition by gender over time (similar to how results are presented in Tables 108 and 109 in the CSR but with groups subdivided by gender and including results of all treatment conditions in both tables). Would you provide these results? It would also be helpful to do the same using the least square mean results for QTcLD based on the analyses that was conducted in reply to our inquiry. Would you also conduct a similar analyses with least square mean results for QTcF and provide the results?

2. We would like to verify if all Phase III trials (-303, -304, -305, -302 and open label trials -702, -703, -704 and -705) used the [redacted]' formulation. If not please clarify.

3. Would you send us more information about the following subjects that would be helpful regarding potential etiologies of these events?

a) Subject 300541 was described in the Clinical Study Report for Study -304 section of the submission as having "pauses" on holter monitor after presenting with syncope, hypotension and bradycardia. Please provide more complete information on this subject (include a

description of the actual syncope that occurred and other relevant information that may help to determine the etiology).

b) A safety alert report submission N182 under IND 65850 for oral ER tablets (OROS) dated 4/3/06 was adescription of a sudden death (after at least 3 months of 12 mg Pal daily in the OL study -701, and was receiving trihexyphenidyl, 2 mg given as needed) in a healthy 24 year old female (subject [redacted]). Please provide more complete information on this subject (include relevant information that may help to determine the etiology). Please also provide a hospital report (e.g. discharge summary) on this subject who died in transit to another hospital and any autopsy report (if one was performed). We are also wondering why this subject was prescribed trihexyphenidyl (e.g. "as needed" for what)?

4. The following paliperidone subjects are some examples which lead us to wondering if we are missing subjects who were adverse dropouts (ADOs), such as subjects who withdrew from the study for reasons related to AEs or due to clinical abnormalities (e.g. subjects who withdrew consent due to AEs, subjects who were withdrawn due to noncompliance in which their noncompliance was due to AEs or subjects that withdrew early for other reasons related to AEs)?

a) Subject 503018 in Study -305 in the original NDA submission was withdrawn due to noncompliance" after 4 days of stopping the study drug (drug stopped on Day 20 and withdrew "due to noncompliance" on Day 24) who had abnormal LFTs on Day 15 and "onward" (elevations of up to approximately 5 times the ULN, first observed on Day 15). Values normalized on Day 29 (9 days post-treatment cessation). This subject was found in the narrative section of subjects but was not checked off in the narrative summary table (preceding the narratives) as having either an SAE or as "premature discontinued." This subject cannot be found in line listings of SAEs or ADOs. The narrative indicates that the elevations in LFTs were not reported as AEs. Please clarify and provide the rationale for how events of elevated LFTs were actually reported in subjects and clarify why the drug was stopped and why the subject was noncompliant.

b. Subject 201803 in Study -303 (33 year old male) had a serious adverse event of tachycardia with increased heart rate first noted on Day 7 of 6 mg daily of Pal treatment compared to baseline values. His baseline supine and standing heart rate values (HR) were 72 and 76 bpm, respectively compared to supine and standing HRs of 106 bpm and 130 bpm, respectively on Day 8 of treatment. Metoprolol treatment was started on Day 10 and given for 11 days. Tachycardia resolved by 14 days. Paliperidone treatment was over 21 days. The subject withdrew from the study on Day 22 "due to consent withdrawn" with an ECG HR of 73 bpm on that day. Why did this subject withdraw consent? This subject was also not checked off under the "premature discontinued" column in the narrative summary table (preceding the narratives) and could not found in the line listings for premature discontinuations in Appendix 2.7.4.3.8.2.1 in the original NDA (in the SCS).

c. Subject 100232 (an ADO due to prolonged QT) is described in the narrative (page 1790 of the SUR) as not being included in the "interim analyses." Please clarify this comment and if this pertains to how this subject was captured in the safety database (e.g. in enumerating ADOs in SUR summary tables or line listings).

d. Subject 300011 withdrew "due to lack of efficacy" and is described in the narrative of the N000 submission as follows:

The subject received paliperidone 12 mg/day; she was discharged from the inpatient hospitalization portion of this study on Day 12 (source: CIOMS). Her symptoms had significantly improved and she was eager to be discharged. At her outpatient therapy on Day 15, she reported that the voices had returned on Day 13 and that she wanted to kill herself (source: follow-up SAE reports). The serious adverse event schizophrenia (increase of symptoms of schizophrenia verbatim) was reported on Day 15; the serious adverse event suicidal ideation (suicide ideation-verbatim) was reported on Day 17 (source: SAE follow-up forms). She went to the emergency room after experiencing a return of hallucinations and wanting to "kill herself." She was admitted to an adult psychiatric unit (source: CIOMS). She took paliperidone 12 mg/day on Day 15 but admitted that there may have been times that she forgot to take the medication (source: SAE follow-up forms). Study medication was held on Day 16, given on Day 17 and then permanently stopped.

She is not checked off in the narrative summary table under "premature discontinued." Was this subject captured in the line listings and summary tables enumerating ADOs (e.g. in Table 34 of the SCS)? If not why and how is this subject different that other subjects with psychotic-related events that were captured in Table 34? Please clarify.

e) Subject 100057 also had AEs that he could not tolerate on the same day of having study medication stopped "permanently on Day 22 as the subject withdrew consent." Refer to the narrative on page 1815. The following are excerpts from the narrative (also see Item II below describing this subject as well):

The subject was discharged from the hospital portion of the study on Day 20. At the scheduled Day 22 visit, he reported side-effects that he "could not tolerate" (restlessness and inability to sleep) (source: CIOMS). Study medication was permanently stopped on Day 22 as the subject withdrew consent. Vital signs were within normal limits but slightly higher than at earlier readings (138/91 mmHg standing; 141/72 mmHg supine); temperature was 36.4 degrees. Laboratory analyses on Day 22 (end of study) revealed a creatine kinase (CK) of 2201 U/L (reference range: 18-198 U/L); all other laboratory values were reported within the normal range. At baseline (Day -2), the baseline creatine kinase value was 186 U/L. The serious adverse events "elevated CK" and "neuroleptic malignant syndrome (acute EPS side effects)" were reported on Day 24 and Day 25, respectively; the elevated CK was considered life threatening.

This subject is recorded on the narrative summary table as only having an SAE and is not checked off as being an adverse dropout but is checked off as an SAE (see the "premature discontinued" column on page 1773)? Please clarify why this subject was not considered an ADO.

Q 5. Why is subject 100057 (an SAE during run-in phase of study -301 found in the narratives) not listed in line listings of SAEs for this study (Appendix 3.5.1) and does not appear to be included in the in-text summary tables of SAEs in the SUR (e.g. Table 31)?

We note a comment about the reason provided as a footnote in the narrative summary table (on page 1773 of the SUR) yet it is still confusing for the following reasons. The subject had SAE of neuroleptic

malignant syndrome reported only 2 days study after the drug was stopped, but was preceded by related AEs that included "muscle stiffness over the entire body" that the subject "could not tolerate" on Day 22. The subject withdrew consent on this same study visit (Day 22). Please clarify why this SAE was not captured in the database.

Are there any other SAEs that occurred after treatment cessation that were preceded by AEs that lead to the SAE that were not captured in the Phase III database (of double-blind and open-label drugs)?

Questions Conveyed to the Sponsor (some responses were received by e-mail and are pending submission to the NDA at the time of this writing)

-----Original Message-----
From: Geter-Douglass, Beth [PRDUS]
Sent: Thursday, June 29, 2006 2:56 PM
To: Karen. Brugge (E-mail)
Cc: Ni. khin (E-mail); Ochalski, Stefan [PRDUS]; Martynowicz, Jadwiga [PRDUS]; Keith. Kiedrow (E-mail)
Subject: RE: Outstanding SCH-1009 Qs & Miscellaneous --EMAIL #1a of 2

Dear Dr. Brugge,

On behalf of Heddie Martynowicz who is on vacation this week, I am acknowledging receipt of your June 28 e-mail with additional questions regarding NDA 21-999.

I am also providing J&JPRD's response to the outstanding question "b" regarding SCH-1009 that was originally sent on June 21 and referred to below as Question #1. Responses to the new questions will be provided to you shortly.

Please find attached the following tables for question "b":

- tecg05b: equivalent for table 108 for each QTc parameter with raw means (descriptive statistics) by gender **Given that this file is too large to send with the others, I will send separately]**
- tecg06b: equivalent for table 109 for each QTc parameter with raw means (descriptive statistics) by gender[Geter-Douglass, Beth [PRDUS]] **Given that this file is too large to send with the others, I will send separately]**

In addition we have for completeness:

- tecg05a: table 108 for each QTc parameter (LSMeans) **[attached]**
- tecg06a: table 109 for each QTc parameter (LSMeans) **[attached]**

Lastly, the LS mean results by gender **[Given that this file is too large to send with the others, I will send separately]**

- tecg06c

Best Regards,
Beth

Beth Geter-Douglass, Ph.D.
Associate Director, Regulatory Affairs
J&J Pharmaceutical Research and Development
609-730-4409 (phone)
609-730-2069 (fax)
609-369-0743 (cell)

Initial Set of Questions Sent to the Sponsor in May of 2006 (See Sponsor's Teleconference Meeting minutes on the following pages that followed this initial request)

We are moving along on the paliperidone review and we also recently received the safety update. We have run into a fairly time-consuming search problem that we were hoping you could help us with. In the original submission there is a line listing of patients with Deaths, Serious Adverse Events (SAE) and Discontinuations due to Adverse Events (DAE) that we found in an appendix to the Summary of Clinical Safety section (SCS). The listing does not provide page numbers or hyperlinks to the exact location for each subject. In-text sections of the SCS sometimes refers to subjects having potentially remarkable safety findings but often does not provide subject numbers and/or exact locations to narratives. Sometimes a hyperlink is provided but it generally goes to a summary table or listing (often a lengthy appendix to the SCS) in which we cannot find the subject number and/or exact location of a narrative of the specific subject in the hyperlinked section.

- So, for the open-label combined-trials safety-dataset, study 301, study 701, would it be possible for you to generate a list of the patients with Deaths, SAE, and DAE along with their verbatim and thesaurus term with a page number reference to the narrative (please make the listing comprehensive to include all deaths, SAEs, DAEs through the cut-off date used for the safety update report submission)?

We also are having trouble reconciling the cases described in the narrative text of the Safety summary with the cases in the datasets. It is common for the cases to be briefly described and enumerated, but there is no way for us to reconcile the descriptions with the actual cases. We are looking at liver effects and syncope and need some help.

- Drug effects on the liver is something that we always look closely at and we have a case that appears to be significant that we could not find described in in-text sections of the SCS (Subject 503018 in the 15 mg Pal group was a 44 year old male with no history or abnormal baseline values suggestive a pre-existing liver disorder who developed approximately 8 times the ULN of ALT and approximately 5 times the ULN of AST with about almost 4 times the ULN of GGT on Day 15 of Pal that resolved to normal values after 9 days (on Day 29) following Pal cessation on Day 20.)

  There are also several patients who had elevated LFTs at baseline and it is difficult to dissect those away from patients who had normal LFTs at baseline and elevations. Would you be able to provide a listing of patients who had normal ALT, AST and bilirubin at baseline who went on to have AST or ALT of >3x and >8X normal along with their bilirubin values when these elevations occurred?

- Syncope and potential pro-arrhythmic effects: Patient 300541 in study 304 is described as having sinus pauses of up to 8 seconds but a description of this subject could not be found in the pro-arrhythmic section of the SCS or in any other in-text section of the SCS.

Subject 201805 in Study -303 (a 33 year old male) had 12 mg daily Pal treatment discontinued on Day 7 who had an SAE of tachycardia that was first noted on Day 4 and reached a HR of 120 bpm supine (124 bpm standing) compared to 71 bpm (per ECG) at baseline (84 bpm supine at baseline). The subject also developed "hypotension" in which Day 4 BP was 100/65 mmHg, supine (115/75 standing) compared to 135/65 mmHg, supine at baseline and decreased further to 85/55 mmHg, supine, on Day 6 (80/50 standing). Supine BP of 115/80 mmHg and HR of 93 bpm on day 7. The tachycardia prolonged his hospitalization. Tachycardia was reported to resolve by 12 days and hypotension by 3 days without treatment. ALT was also reported to be "increased" during the study.

Subject 201803 in Study -303 (33 year old male) had a SAE of tachycardia with increased heart rate first noted on Day 7 of 6 mg daily of Pal treatment compared to baseline values while BP generally did not change from baseline vales. This subject was not described as having orthostatic hypotension (on page 146 of the CSR). His baseline supine and standing heart rates were 72 and 76 bpm, respectively compared to supine and standing heart rates of 106 and 130, respectively on Day 8 of treatment. Metoprolol treatment was started on Day 10 and given for 11 days. Tachycardia resolved by 14 days. Paliperidone treatment was over 21 days, then the subject withdrew from the study on Day 22 "due to consent withdrawn" with an ECG heart rate of 73 bpm on that day.

We are interested in a listing of patients that were asymptomatic at baseline but who went on to have syncope, symptomatic bradycardia or tachycardia or symptomatic hypotension. Would it be possible for you to make a listing of these patients (with whether they were SAE, DAE or both along with their verbatim and thesaurus term) and a page number reference to the narrative?

Follow-up Teleconference Minutes (Sponsor's Version) of a 5/15/06 Teleconference between the Sponsor and Team Leader Dr. Paul Andreason and Reviewer Dr. Karen Brugge (with some Responses in a N005 6/15/06 Submission)

-----Original Message-----
From: Martynowicz, Jadwiga [PRDUS] [mailto:JMartyn1@PRDUS.JNJ.com]
Sent: Monday, May 15, 2006 9:23 PM
To: Kiedrow, Keith
Subject: NDA 21-999: Summary of 15 May 2006 Teleconference

Dear Keith,

Thank you for arranging this teleconference. As promised, here is our summary of key outcomes from the meeting. Please share with Drs. Brugge and Andreason and let me know if there are any differences in understanding.

Attendees from FDA: Paul Andreason, MD; Karen Brugge, MD; Keith Kiedrow, PharmD.

Attendees from J&JPRD: Peter Briscoe, MD; Denise Brown; Jackie Brown; Linda Carter; William Clayton; Joseph Donato, Beth Geter-Douglass, PhD, Michelle Kramer, MD, Pilar Lim, PhD; Heddie Martynowicz, MS; Anna Mendlin, PhD; Wayne Napoliello, Paul Sokol.

* We agreed that FDA Medical Reviewers may contact J&JPRD at anytime with further questions resulting from their ongoing review of the NDA. The primary contact will be Heddie Martynowicz. Contact information for Heddie is provided below:

Tel: 609-730-7028
Cell: 609-509-1043
Fax: 609-730-3091
Email: jmartyn1@prdus.jnj.com

* J&JPRD will update and combine the tables currently provided in front of the narrative sections of the 4-month Safety Update to add the following information for each subject: verbatim and thesaurus terms and page numbers for each narrative included in the 4-month Safety Update through the cut-off date of November 1, 2005. The resulting comprehensive table will be organized as follows: R076477-SCH-R076477-301, R076477-SCH-701 and followed by pooled open-label trials (R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705).

* FDA clarified that the data displays requested below are needed to complete their standard safety assessment:
* An incidence table by treatment group will be provided for subjects in the double-blind studies that were included in the original NDA (R076477-SCH-303, R076477-SCH-304 and R076477- SCH-305) with ALT and/or AST values >3 times the upper limit of normal (who had normal AST, ALT and bilirubin values at baseline). A separate incidence table will be provided for the elderly study (R076477-SCH-302).
* A listing of subjects with ALT and/or AST values >8 times the

upper limit of normal (who had normal AST, ALT and bilirubin values at baseline) and existing narratives previously submitted to the NDA will be provided for all safety datasets including those submitted in the original NDA as well as those included in the 4-month Safety Update through the November 1, 2005 cutoff date.

* A listing of those subjects with syncope, symptomatic bradycardia, symptomatic tachycardia or symptomatic hypotension (asymptomatic at baseline) will be provided for all safety datasets including those submitted in the original NDA as well as those included in the 4-month Safety Update through the November 1, 2005 cutoff date. For those subjects with SAE's, deaths or discontinuations due to adverse events, existing narratives previously submitted to the NDA will be provided for ease of review. The methodology used for selecting subjects for this listing will be described.

* The above items will be provided to FDA as soon as each response becomes available and will be submitted as Review Aides. The timelines for providing FDA responses to these requests are in preparation.

* The same requests will be applied to the 7-month Safety Update. However, the information will be limited to only the new safety data available after the cutoff date of the 4-month Safety Update.

Thank you for a very informative and productive discussion. I am looking forward to working with you, Dr. Brugge and Dr. Andreason in addressing any further questions/requests and facilitating completion of FDA's review of this NDA. In addition, please note that J&JPRD is willing to assist in addressing questions as they arise from any of the other FDA Review Teams.

Best regards,

Heddie

Heddie Martynowicz, M.S.
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The Sponsor's Minutes of 5/23/06 Teleconference with Some Responses in a N005 6/15/06 and Submission

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Regulatory Affairs **Record of Contact**

EDMS-PSDB-5573941

Date of Contact: 23 May 2006 **Date of Report:** 25 May 2006

Health Authority/Division:
Center for Drug Evaluation and Research/Division of Psychiatry Products

Product: R076477 (RWJ16232411) (paliperidone)
NDA No.: 21-999

Health Authority Contact:
Name: Keith Kiedrow, Ph.D.
Title: Project Manager

Prepared by:
Name: Heddie Martynowicz, MS
Title: Director, Regulatory Affairs

Health Authority Attendee(s):
Name: Paul Andreason, MD
Title: Psychopharmacology Team Leader

Name: Karen Brugge, MD
Title: Medical Reviewer

Company Attendee(s):
Name: Heddie Martynowicz, MS
Title: Director, Regulatory Affairs

Subject: QUESTIONS RECEIVED VIA TELEPHONE FROM DRS. ANDREASON AND BRUGGE ON 23 May 2006 REGARDING NDA 21-999 AND FOLLOW-UP E-MAIL FROM DR. BRUGGE

1. **Vital signs**: Study 1009: Did you collect vital signs at Tmax in this study? If no, do we have information from any other Ph 1 study (preferably with the to be marketed formulation) where we may have collected vital signs and EKGs at Tmax.

2. **Confounding factor analysis**: Study 1009: Looking for role of confounding variables, such as gender, concomitant medication or pre-existing cardiac condition. This info is not found in SCS. Also would like to see raw mean results presented in Table 109 in SCS.

3. **Logic for laboratory data displays in the SCS**: We provide in the SCS incidence of outliers for a variety of laboratory parameters. However, this list is not comprehensive. FDA wants to understand why we chose to present only those and not the other laboratory parameter in the SCS. Is it because there were no outliers in those parameters? If this is not the case where can they find the rest of the data?

4. **Suicidality**: SCS Section 2.1.6.1.1 provides a search of all terms that may be indicative of suicidality. FDA is having a hard time reconciling this list with cases included elsewhere. They want to understand what patients where excluded and why. They make references to cases described on p.109, 104, 96, 95 and specific references to patients from 304 study: 300397 and 300301. They don't understand why these cases should be excluded from list and dismissed, as terms are suggestive of suicidality. And they don't see info of any pre-existing suicidality at study entry.

5. **CPK**: We mention in the SCS that we have observed inconsistent elevations in CPK in our Ph 3 schizophrenia data. We also offer an explanation that this is indicative of the

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EDMS-PSDB-5573941

schizophrenia population (not due to extra pyramidal effects of the drug or other effect of the drug). However, when looking at the Ph 1 data, FDA notes that there are also elevations in healthy subjects and that the greatest increases in CPK occur in the paliperidone high dose group. FDA is looking at the SCS, which includes information from 17 pooled phase 1 studies. In this section, there are various subgroups within that data set, including placebo, low dose OROS, high dose OROS and other. FDA wants to understand why there are elevations in healthy subjects? They are looking for pooled information (a) descriptive statistical results and (b) incidence of outliers for these subgroups from the pooled data set. FDA is particularly interested in seeing results for the placebo group.

Follow-up e-mail from Dr. Brugge to Ms. Martynowicz on 23 May 2006:

I just found a few examples in which I cannot find results in summary tables on a clinical parameter for a given treatment condition (in this case it's the IR Paliperidone treatment condition) for the Phase I healthy subject (pooled) safety dataset. See appendix 2.7.4.3.1 as an example on page 3611 in which creatine kinase results are not shown for placebo treatment condition/group and also for some other treatment conditions/groups. Note that these groups have results for other parameters but not for all parameters. Look at page 3627 in Appendix 2.7.4.3.2 for another example where creatine kinase and other parameters are not shown for the "Pali IR" subgroup but results on some other parameters are shown.

A Question to Which a Response was Submitted (N007 6/27/06)

During the 15 May 2006 teleconference, the FDA requested the following information:

> Please provide a listing of subjects with symptomatic bradycardia, tachycardia, hypotension, orthostatic hypotension, and syncope (asymptomatic at baseline) for all safety datasets through November 1, 2005. For those subjects with serious adverse events, deaths, or discontinuations due to adverse events, it was agreed that existing narratives previously submitted to the NDA would be provided with the response to this request.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Brugge
7/21/2006 07:43:58 PM
MEDICAL OFFICER

Ni Aye Khin
8/31/2006 02:59:57 PM
MEDICAL OFFICER
I agree that this NDA be considered approvable; see memo to file for additional comments.