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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-825

Medical Review(s)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-825
Sponsor: Pfizer
Drug: : (ziprasidone)
Material Submitted: Response to Nonapprovable Letter (3/10/00), Responses to Request for Information (4/6/00, 5/19/00, 5/22/00), Safety Update #3 (6/2/00)

I. Background

Summary
Ziprasidone is a new antipsychotic which has serotonin ($5\text{-}HT_{2A}$) and dopamine (D_2) antagonist properties and received a non-approvable on 6/17/98 for the original NDA submission. The nonapprovable letter delineated concerns regarding ziprasidone's safety data which demonstrated a dose dependent QTc prolongation observed in the short-term placebo controlled studies, and that this represented a risk of "potentially fatal ventricular arrhythmias that is not outweighed by a demonstrated and sufficient advantage of ziprasidone over already marketed drug products." In response to this nonapprovable letter, the sponsor designed and conducted Study 054 which would characterize the QTc effects of currently marketed neuroleptic agents (risperidone, olanzapine, haloperidol, thioridazine, and quetiapine) in an effort to compare ziprasidone's ability to prolong the QTc with these other neuroleptic agents.

The sponsor's response to the nonapprovable letter was submitted on March 10, 2000 and included the study report of Study 054; the submission included a small amount of summary safety information up to February 5, 1999. In subsequent submissions, at FDA's request, the sponsor submitted narratives of all serious adverse events, cases of overdose, updated mortality tables and selected discontinuations occurring from May 15, 1997 to February 5, 2000, and all deaths in the entire NDA data base. The cut-off date for the safety data base reviewed in this document is February 5, 2000.

Administrative History

The original consultations obtained by FDA Cardiorenal Division written by Charles Ganley, M.D. (1/13/98 &11/24/97) stated that "if ziprasidone does prolong the QT interval, as the short term, fixed-dose, placebo controlled trials suggest, then some patients will be at risk for the development of torsades de pointes based on the experiences with other QT prolonging drugs [1/13/98]." Dr. Ganley recommended that, "unless efficacy data suggests superior benefit over currently available drugs, ziprasidone should be considered for second line therapy with adequate warnings of risk associated with drugs that prolong the QT interval [11/24/97]."

In his memo of May 14, 1998, Thomas Laughren, M.D., Team Leader for Psychiatric Drug Products, Division of Neuropharmacological Drug Products expressed concern for the approval of ziprasidone at the recommended doses because of the issues of QTc prolongation, and recommended approval of ziprasidone at a lower dosing range (20-40 mg bid). He also recommended that ziprasidone "be made available only as a second line drug with very strong labeling." Dr. Laughren recommended that labeling include a contraindicated use with other drugs that prolong the QTc interval, and "a bolded and boxed warning regarding QTc prolongation...and... [recommendations] for screening and monitoring (ECGs; serum potassium; and Holter monitoring for symptomatic patients). "

In a memo of June 1, 1998, Paul Leber, M.D., then Director of the Division of Neuropharmacological Drug Products, stated that he may have considered recommending

approval if ziprasidone had demonstrated a "unique benefit or advantage not provided by already marketed antipsychotics....however, the only evidence...that we have makes a point to state that ziprasidone's comparative performance (Study 115) supports a conclusion that it is less efficacious than haloperidol, a long marketed antipsychotic drug." Dr. Leber recommended a nonapprovable action.

The nonapprovable letter of June 17, 1998 asserted that a sufficient advantage over currently marketed antipsychotics had not been demonstrated that could outweigh the risk of potentially fatal arrhythmias because of the demonstrated QTc prolongation. The letter went onto say that ".... we would find QTc prolongation at maximum blood levels in the 5-10 msec range, with adequate assurances that there are very few outliers and that there are no factors that lead to substantially greater values in individuals (such as drug-drug interactions), sufficiently reassuring...to support approval of a new antipsychotic such as ziprasidone."

Advisory Committee Meeting

A Psychopharmacological Drug Advisory Committee meeting was held on July 19, 2000 to discuss the NDA 20-825 for Zeldox (ziprasidone hydrochloride capsules) sponsored by Pfizer. The following summary is based on the Flash minutes distributed July 20, 2000 (full transcript to be available after August 20,2000 at < http://www.fda.gov/ohrms/dockets/ac/acmenu.htm >).The majority of the committee voted for the approval of ziprasidone based on the safety information presented. There were concerns expressed regarding the lack of dose escalation data; it is unknown what would occur when ziprasidone might be used as a concomitant medications in which the dose levels increased significantly, and whether or not there could be an additive effect of QTc when administered with another drug which prolonged the QTc. There was consensus that there needed to be strong warnings regarding the potential for fatal arrhythmias, but no clear consensus of how that should be communicated to practitioners.

II. Updated Clinical Data

The original NDA clinical review discussed the sponsor's primary integrated safety data base which included 2588 patients participating in Phase II/III studies as of a cut off of May 15, 1997. This original safety data base incorporated data from both the original NDA submission (cut-off 10/31/96) and a four month safety update (cut-off 5/15/97).

Updated Primary Integrated Database

This review will cover the sponsor's primary integrated safety data base with a new cut-off date of February 5, 2000. It is also noted that the sponsor has included trials conducted in Japan in this new integrated safety data base; whereas in the original NDA submission, Japanese studies were not included in the integrated safety data base.

The following table shows the number of patients and patient-years exposure of the primary integrated data base for Phase II/III oral ziprasidone trials as of the cut-off date of February 5, 2000:

TREATMENT GROUP	N	Patient-Years
Ziprasidone (cut-off: 2/2000)	4571	1732.6
Placebo	605	91.8
Haloperidol	1071	298.6
Risperidone	426	196.4

Since the original NDA review cut-off date of May 15, 1997 to the most recent cut-off of February 5, 2000, ziprasidone has had an additional 961 patient years exposure; the additional patient years exposure for the other treatment groups are as follows: 1) placebo: 39, 2) haloperidol:167, and 3) risperidone:91.

Of the 4571 patients exposed to oral ziprasidone, 603 patients participated in the oral portion/extension to an IM study, 991 patients received ziprasidone for longer than 6 months, and 605 patients were exposed to ziprasidone for at least one year.

Deaths

As of the sponsor's cut off date of February 5, 2000, there have been a total of 50 deaths. Please refer to Appendix I for a listing of all deaths known to occur in patients exposed to ziprasidone. Since the original NDA review of 4/30/98 (cut-off of 5/15/97), there have been an additional eleven deaths which occurred within 30 days or less of the patients' discontinuation of ziprasidone, making a total of twenty-eight deaths occurring within 30 days.

Of these twenty-eight deaths, eleven of them could be considered as sudden unexpected deaths in which the patients were either found dead or died within 24 hours of onset of their symptoms associated with death. There are four additional sudden and unexplained deaths since the last ziprasidone NDA review: 1) Subject 108E-7160157, a 49 y.o. male found unresponsive in the bathroom; the investigator is reported to think the cause of death was an acute myocardial infarction based in laboratory tests, yet, no autopsy or coroner's report were available, 2) Subject Yale-9990040, a 34 y.o. male with Tourette's Syndrome who was found dead in his truck; an autopsy report (submitted 6/15/00 under IND [redacted] stated that the cause of death was occlusive coronary atherosclerosis, 3) Subject NY-97031E0054, a 51 year old patient found dead, but no coroner or autopsy report was located in the sponsor's submission, and 4) JP-966024500811, a 50 y.o. Japanese male who experienced palpitations and nausea on the second day of ziprasidone treatment and was subsequently treated with an antibiotic, (flomoxef) was reported as dead by the police four days later. (Please refer to Appendix I for further detail).

The following table updates the mortality rates for patients in the Phase II/III trials of the integrated safety data base who have died during the study or within thirty days of discontinuing treatment with ziprasidone; as in the previous review, the placebo group appears to demonstrate the highest mortality.

Mortality rate for Phase II/III clinical programs in ziprasidone NDA 20-825

DRUGS	Number of Patients [1]	Patient-years exposure [1]	Total # deaths	# deaths ≤ 30 days	Crude mortality rate [2]	Mortality per 100 patient-years [2]
Ziprasidone (cut-off: 2/2000)	4571	1732.6	50	28	0.006	1.62
Placebo	605	91.8	10	5	0.008	5.45
Haloperidol	1071	298.6	3	3	0.003	1.00
Risperidone	426	196.4	2	1	0.002	0.51

[1] Includes integrated safety data base (which has been redefined to include Japanese studies), Study 105 (IM: ziprasidone n=11; placebo n=12) and Study 120 (dementia: ziprasidone n=12)
[2] Based on # of deaths ≤ 30 days

The tables below updates the sudden unexpected death rate. With the increased patient years exposure since the last NDA, it appears that there have been a decrease from 9.1 SUD per 1000 (n=772) to 5.8 SUD per 1000 for the ziprasidone treatment groups.

Rate of Sudden Unexpected Death* (SUD) in Ziprasidone NDA 20-825

DRUGS	Number of Subjects [1]	Subject-years exposure	# Sudden Deaths	SUD per 1000 subject years
Ziprasidone	4571	1732.6	11#	6.3
Placebo	605	91.8	0	0
Haloperidol	1071	298.6	0	0
Risperidone	426	196.4	1	5.1

*Sudden Unexpected Death (SUD) refers to subjects found dead or who died within 24 hours of symptoms Refer to Appendix I for listing of deaths considered to be SUD.
#Does not include subject 115-6940394; please refer to the text of Section 8.1.1 of NDA review of 4/98.
[1]Includes integrated safety data base, Study 105 (IM: ziprasidone n=11; placebo n=12) and Study 120 (dementia: ziprasidone n=12)

However, when updating the SUD comparison rate of ziprasidone and the most recently submitted antipsychotic NDAs (table below), it appears that both ziprasidone and sertindole continue to surpass the SUD rate of olanzapine, risperidone, and quetiapine:

Rate of SUD in most recently submitted antipsychotic NDA data bases *

DRUGS	Subject-years exposure	# Sudden Deaths	SUD per 1000 subject years
Ziprasidone (cut-off: 2/2000)	1733	11	6.3
Ziprasidone (orig. cut-off 6/98)	772	7	9.1
Sertindole	476	5	10.5
Olanzapine	1122.2	4	3.5
Risperidone	508	1•	1.9•
Quetiapine	865.3	1	1.1

*Sources are the current NDA 20-852 and Review of Clinical Data: *General Characteristics of the Deaths in the NDAs for Olanzapine, Risperidone, Quetiapine and Sertindole* by Greg Burkhart, M.D. (HFD-120: 3/3/98)
•Correction from NDA Review of 4/30/98 to exclude a SUD during drowning episode.

There may be limitations to interpreting a comparison of the sudden deaths across data bases. The system of assigning sudden deaths was not tested for consistency with blinded readers, and the definition of sudden death may not have been consistently applied for each NDA data base, not to mention the inherent difficulty in being able to accurately assign the true cause of death in many cases.

Overdose Experience

The sponsor did not define what they considered to be an overdose. The table below includes cases in which the overdose was thought to include ziprasidone. Please see Appendix II for cases in which the patient was currently being treated with ziprasidone, but the overdose was believed to be with a different medication.

Summary of overdoses with ziprasidone

Patient #	Age/ Sex	Overdose Mg	Concomitant medications	Comments
116B5290019	49/M	240 mg	Valproic acid	Intentional O/D. Hospitalized because of command hallucinations. Unclear what associated effects of O/D were. CT of head for chronic headaches and dizziness was WNL.
127E5810001	43/F	640 mg		Patient reported O/D. Hospitalized for moderate sedation.
301E1950995	21/F	24 day supply—dose unclear		Admitted to hospital after repeated vomiting. Received gastric lavage.
NY970020018	50/M	3240 mg		Initially reported as coma due to O/D; sponsor revised report to state that patient was drowsy and minimally sedated. QTc readings (central reading): Baseline QTc=454; Day of event: maxQTc=478
116B5950006	64/F	360 mg		Narrative not located. Table states that patient accidentally took ziprasidone. No QTc prolongation evident one day after incident.
116B5950014	26/M	Day 1: 400 mg Day 2: 480 mg		Narrative not located. Sponsor's table states that patient accidentally took ziprasidone with no QTc prolongation one day after incident.
NY970020105	29/F	Unknown		Patient reported to take O/D of ziprasidone (amt. unknown). Taken to hospital and released that day. No details submitted.

It appears that nausea, vomiting and sedation were the most prominent effects of overdose. There were no apparent sequela from overdoses with ziprasidone. There were also an additional 6 patients who were in blinded treatment listed as taking overdoses; the narratives did not report any remarkable events or treatments.

There were no deaths reported associated with an overdose of ziprasidone.

It is difficult to make definitive safety conclusions from the above overdose data. In most cases the serum level was not provided, and it was unclear if any of these overdoses were witnessed. At best, the above data speaks to concerns about an single elevated dose rather than allowing for conclusions to a longer exposure to high levels of ziprasidone.

Adverse Events

Since the original NDA review, additional data covered in this review has been collected from open label studies and three placebo controlled studies (Study 307:a 52 week flexible dose placebo controlled trial and Studies 601 & 602: placebo controlled studies being conducted in patients with mania). Data from these studies has been included in the serious adverse events and the discontinuation, but because these three placebo controlled studies are not yet completed and analyzed, there is currently no new information to contribute to the common adverse events profile. The remainder of this section will focus on significant adverse events, serious adverse events, and some adverse events which lead to premature discontinuations.

Upon request, the sponsor provided updates for the adverse events of syncope, rash and seizure as follows: 1) updated incidence rate for episodes of rash is 4.5% or 173 of 3834 patients, 2) for syncope, the rate is 0.57% (22/3824), and 3) for seizure, the rate is 0.39% or 15 of 3834 patients treated with ziprasidone.

Please refer to Appendix III which is a modification of the sponsor's table of all serious adverse events as submitted on May 22, 2000 covering the period of May 15, 1997 to February 5, 2000. All narratives submitted for each patient were read, and, for the most part, the sponsor's listing of the event accurately reflected the narrative.

Most of the serious adverse events observed in this report period were also observed in the original NDA submission, and not unexpected. Of note was a 25 y.o. patient (Subject #128-601E-189-0077 or 128-601E-0540-0077) who had an episode of neutropenia with a WBC =2.3 (NL range: 4.1-12.3) in the first month of treatment with ziprasidone; this neutropenia resolved after hospitalization (treatment unclear), and the patient was reported to have continued taking ziprasidone throughout and after this episode.

The following patient with a serious adverse event deserves mention:

Subject #302E-057-0456: 46 y.o. male with schizophrenia experienced weakness and **chest pain** after eight months of ziprasidone treatment. After being treated with isosorbide dinitrate in the hospital, he experienced a **syncopal event with bradycardia** (26 bpm). The centrally read ECGs three days prior to and one week after the event did not demonstrate any QTc prolongation; however, there were no ECGs submitted during the episodes of chest pain or bradycardia/syncope, and none located in the case report form requested from the sponsor (submitted 7/14/00) .

Discontinuations Due to Adverse Events

A review of the discontinuations revealed one notable case of an event not previously observed in the original NDA data:

Subject 601-0520-0027: 38 y.o. male experienced **priapism** after twelve days of ziprasidone treatment. The event resolved on the same day that the study drug was discontinued suggesting a temporal relationship of this event to treatment with ziprasidone.

Other reasons for discontinuations during this safety period were also observed in the original NDA submission and not unexpected (please see Appendix IV for a list reasons for discontinuations for this review period).

QTc Outliers Reported by the Sponsor

In the reporting period covered by this review (5/15/97 to 2/5/00), the sponsor reported the following additional patients who had a prolonged QTc, but the readings of whether there was a QTc ≥ 500 msec depended on which central reader interpreted the ECG. The sponsor employed two central ECG readers:

Subject 121-590-0362: 48 y.o female with hypertension, had a QTc of 504 msec on Day 4, the first day of oral dosing after treatment with IM ziprasidone: QTc readings are in the following sponsor summary table:

Study Day	Date	Dose (Time)	ECG Time	QTc (GDXI)	QTc (PRW)
Baseline	20 January 1997			420 msec	424 msec
Day 3	23 January 1997	5 mg IM (15:30)	--	--	--
Day 4	24 January 1997	20 mg PO (9:00)	9:38	504 msec	442 msec
Day 7	27 January 1997	20 mg PO (9:00)	10:31	462 msec	438 msec

Subject 126-701-0079
/127E-701-0003

53 y.o. male with baseline ECG reading of left bundle branch block had the following ECG readings while being treated with ziprasidone:

Study Day	Date	Dose (Time)	ECG Time	QTc (GDXI)	QTc (PRW)
Baseline	25 June 1997			426 msec	520 msec
Day 2	26 June 1997	20 mg IM (3:00)	12:53	423 msec	522 msec
Day 2	26 June 1997	80 mg PO (?)	--	--	--
Day 6	30 June 1997	120 mg PO (?)	--	--	--
Day 7	1 July 1997	40 mg PO (?)	8:45	490 msec	468 msec

Subject 97-R-585-3027-3227: 37 y.o. female diagnosed with schizophrenia with an ECG showing a QTc=513 (later re-read by PRW as a QTc=434) after 3 months of treatment with ziprasidone. She continued treatment with ziprasidone 80 mg bid, started divalproex sodium as a mood stabilizer, and one month later reported experiencing two syncopal events while a new ECG showed nonspecific T wave changes and a QTc=387 msec.

As with the case above, there were numerous ECGs in the NDA data base, which, when locally read had a QTc ≥ 500 msec, but when re-read centrally (presumably blinded), the QTc intervals did not exceed 500. The sponsor listed the following as previously reported cases:

Subject 117-648-0167: 39 y.o. male discontinued treatment for a QTc of 503 msec on day 7 of ziprasidone treatment (80 mg/day). Baseline QTc=466 msec.

Subject 301-311-0977 28 y.o. female diagnosed with schizophrenia whose death occurred two days after discontinuing ziprasidone. Upon discharge from the study, ECG changes were consistent with subendocardial ischemia with substernal pinching sensation. ECG after last AM dose of 60 mg ziprasidone showed Qtc=391 msec. After receiving 200 mg thioridazine that afternoon two ECGs showed QTc= 518 &593 msec (timing unclear). Patient died the next day with cause of death reported to be myocarditis.

III. Pfizer's Response to the Nonapprovable Letter.

Study 054

As a response to the nonapprovable letter of June 17, 1998, the sponsor conducted Study 054, an open label, six arm study designed to assess the effects of ziprasidone on the QTc interval compared to currently marketed antipsychotics (risperidone, olanzapine, haloperidol, thioridazine, and quetiapine) at the maximum recommended dosage. This design allowed for assessment of ECGs at the time of maximum concentration (tmax) for each antipsychotic in the absence and presence of an appropriately chosen CYP450 inhibitor. The study was conducted in 185 patients (approximately 30 per treatment group) aged 18-59 y.o. diagnosed with a psychotic disorders (with no acute exacerbation within 3 months).

This study's results were reviewed in depth by Maryann Gordon, M.D. from the Division of CardioRenal Drug Products (Consult: 6/14/00). The following tables (based on tables from Dr. Gordon's review and the sponsor's table 5.2.2.1.1) summarize the results of Study 054:

Mean change from baseline in the **absence** of a Metabolic Inhibitor

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QTc*	20.6 msec	10.0	6.4	14.5	35.8	4.7
Heart Rate	4.6 bpm	6.4	6.5	11.2	5.7	-2.9
QT	7.0 msec	-11.8	-9.3	-12.2	19.7	12.5

*Using Bazett's formula

Mean change from baseline in the **presence** of a Metabolic Inhibitor

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QTc*	20.4	3.2	5.3	19.7	28.0	8.9
Heart Rate	3.6	0.5	3.0	15.1	-2.1	-5.7
QT	9.9	1.1	-1.8	-15.8	33.3	22.5

*Using Bazett's formula

From the above tables, it can be seen that ziprasidone demonstrates a QTc mean change from baseline that is higher than the recently marketed atypical antipsychotics and haloperidol, and that thioridazine demonstrates the greatest QTc mean change from baseline. Quetiapine may appear to have a relatively high QTc change from baseline; however, it has been proposed that Bazett's formula may not be accurately applied to drugs which have an appreciable increase in heart rate. In a preliminary review of Study 054, Greg Burkhart, M.D., M.S. (1/11/00), points out that the "for drugs that cause an increase in heart rate, one would expect the QT to decrease, as occurred with risperidone, olanzapine, and quetiapine. However, for thioridazine and ziprasidone, both of which increase in heart rate, the QT increased. (Haloperidol also had an increase in QT, but the heart rate decreased from baseline in this group so that the increase in QT would be expected.)" It can also be seen from the above tables that there is no appreciable change of QTc for ziprasidone in the presence of a metabolic inhibitor. (Please see Dr. Gordon's and Dr. Burkhart's reviews for more result details).

Considering the results of this study and the findings of a dose dependent increase in the QTc from the placebo controlled studies, Dr. Gordon stated that ziprasidone increased the QTc from baseline on an average of 10-20 msec, compared to thioridazine's change of approximately 36 msec, and the 21 msec QTc prolongation observed with sertidole (an antipsychotic withdrawn prior to marketing in the U.S. because of concerns regarding sudden deaths observed in the UK's post-marketing reports). The slight increase in blood level changes observed for ziprasidone in the presence of a metabolic inhibitor were negligible enough to not present an additional concern.

Dr. Gordon concluded that Study 054 demonstrated that ziprasidone and thioridazine adversely affect cardiac repolarization as seen by their ability to prolong the QTc and QT intervals in a concentration-related manner, and that some patients would be at an increased risk of potentially fatal arrhythmias when exposed to either of these drugs. Considering the characteristics of QTc prolongation as an added risk, Dr. Gordon recommended that a drug with this profile either not be marketed or be used only as second line therapy.

In an effort to establish some benefit for the use of ziprasidone as an antipsychotic, the sponsor also provided data showing that patients had a decrease in total cholesterol and triglycerides in the ziprasidone group compared to the other antipsychotic treatment groups in this open label

study 054. However, it is noted that in the short term placebo controlled trials, the ziprasidone groups were shown to have statistically significant increases in cholesterol and triglyceride levels when compared to placebo with respect to numbers of patients exceeding threshold values.

Also of interest in this study is that the mean serum concentration of a dose of ziprasidone 80 mg bid was 49 ng/ml on Day 2, and increased to 171 ng/ml at steady state (Day 8). In the presence of the 3A4 metabolic inhibitor ketoconazole, the mean ziprasidone concentration increased to 224 ng/ml.

Data Regarding Weight Changes

The sponsor claims that there is a beneficial weight gain profile to ziprasidone compared to other antipsychotics. However, in the placebo controlled studies, there was an increase of ≥ 7 % weight gain observed, which was statistically significant compared to placebo. The only head-to-head comparison study which the sponsor describes is Study 054 (an open label study) in which 2 patients (5.9%) in the ziprasidone group were observed to have a weight gain ≥ 7 % while 1 patient (3.1%) in the haloperidol group, 6 patients (23.1%) in the olanzapine group, 5 (18.5%) in the risperidone group, 3 patients (10.3%) in the quetiapine group, and 3 patients (9.7%) in the thioridazine group showed a weight gain ≥ 7 %; these results are difficult to interpret as there was no placebo control group, and it was a short term study (less than 28 days) in a relatively small sample (25-35 patients in each group). In the 52 week placebo-controlled study 303, two of the three ziprasidone treatment groups showed an higher percentage of patients with weight gain when compared to placebo (ziprasidone 20 mg bid: 11% gained ≥ 7 %, in 40 mg bid group: 4.3 %, in 80 mg bid group: 8.6 %, and placebo: 4.3 % patients gained ≥ 7 %); it is noted that 46% of the patients in the ziprasidone group and 20% of patients in the placebo group completed this study. Other studies sited by the sponsor were open label studies, and not located in the NDA submissions.

Labeling

If approved, the following are recommended revisions to the sponsor's proposed labeling (3/10/00):

1. The sponsor's proposed statements regarding a pharmacokinetic profile in the pediatric population based on a small study (n=25) of pediatric patients with Tourette's Syndrome (under Special Populations). These findings are preliminary and efficacy for schizophrenia (the labeled indication) has not been tested in children or adolescents, and it could be misleading to include this data. It is also recommended that the labeling not include outcomes of this pilot study of Tourette's Syndrome in children/adolescents until the sponsor has proven safety and efficacy in this population for the proposed indication of schizophrenia (under Clinical Trials: Pediatric Studies section of sponsor's proposed labeling).

2. Under Contraindications, it may be beneficial to add several other drugs by name which also prolong the QTc that should not be used concomitantly with ziprasidone such as quinidine, pimozide, thioridazine, sotalol, moxifloxicin, and sparfloxacin. It would be prudent to also contraindicate this medication in patients with congenital long QT syndrome, history of cardiac arrhythmias, uncompensated heart failure, and acute myocardial infarction, as the sponsor has proposed.

3. Under the Warnings Section, it is recommended that the labeling resemble the new proposed labeling for Mellaril, with a bolded, black box delineating concerns regarding ziprasidone's effect on the QTc interval, and making the language strong enough that this drug would be used as a second line with emphasis that efficacy has not been established in the treatment resistant schizophrenic population.

4. Under the Precautions Section, it is recommended that the following subsections be added to the sponsor's proposed labeling: rash, orthostatic hypotension, potential for cognitive and motor impairment (somnolence), and dysphagia to reflect both the integrated safety data base of ziprasidone and standard language in the labeling of antipsychotic medications.

   Because of one case of priapism observed in this data base, it is recommended that priapism be added to the precautions section of the labeling.

5. In the Information to Patients, it is important that patients be alerted to the risks involved with syncopal events and their need to seek medication attention if an episode occurs. Other information should include the current understanding of drugs which prolong the QTc interval, as ziprasidone does, to cause potential fatal arrhythmias, and sudden death, in addition to syncope. It may also be of some aid to have a patient insert with every prescription to maximize the efforts to educate patients and families. Ideally, there would be a mechanism to insure informed consent.

6. Under Laboratory Tests, it may be prudent to recommend patients obtain screening tests of an ECG and electrolytes to rule out circumstances which may leave patients more vulnerable to the cardiac adverse events associated with drugs which prolong the QTc interval. It might also be prudent to recommend routine ECGs to rule out any new onset ECG changes as a result of ziprasidone exposure.

7. Under Drug Interactions, it should be emphasized that there is no data regarding ziprasidone's effect when co-administered with another drug which prolongs the QTc, and that this combination should be avoided at the current time.

8. Because the NDA for [redacted] has been withdrawn at this point, all references to the [redacted] should be removed from the sponsor's proposed labeling.

IV. Financial Disclosure Information

The sponsor submitted a certification of Financial Interests and Arrangements of Clinical Investigators in Section 19.3 entitled Financial Disclosure Information.

There were a total of 5 sites in the study including four U.S. sites (794, 602,782, 529) and one site in South Africa (529). Site 794 had 2 principle investigators and 13 subinvestigators; site 602 had 1 principle investigator and 9 subinvestigators; site 782 had one principle investigator and 13 subinvestigators; site 529 had one principle investigator and 6 subinvestigators, and site 5006 had 1 principle investigator and 6 subinvestigators.

[redacted]

Otherwise, there were no other specific financial disclosures made by other investigators. No disclosures were able to be collected from six individual subinvestigators who were no longer working at the study sites and either had no forwarding address or did not respond to forms sent to their forwarding address. The sponsor's Director of Medical Finance signed the Form 3454 certifying that there was no financial arrangement made with investigators that could affect the

outcome of the study as defined in 21 CFR 54.2(a), and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Because of the disclosed by , a cursory review of the ECG data of Site compared to other sites was performed. From this informal brief review, results from Site appeared to be consistent with results from the other sites. In a telecon of 7/12/00, Dr. Charles Ritrovato of Pfizer stated that he was unable to provide information at this time as to how many patients Dr. had enrolled in this study site, but it was noted that Dr. was one of 13 subinvestigators at this site. Based on the limited information available at this time, there does not appear to be a noticeable difference in the findings of Site compared to other sites. It cannot be definitively determined if Dr. potential financial conflict was problematic or not; however, the total results from the study site in which Dr. was a subinvestigator did not appear to distort the final outcome of Study 054 in any obvious manner.

Efforts on the sponsor's part to minimize bias of Study 054 included randomization of subjects through the use of a tele-randomization system operated in the UK. Also, the sponsor utilized a blinding process in which ECG tracings from each site were transmitted electronically to were they were blinded and then forwarded to the central reader at for interval determinations.

V. Foreign Marketing

Ziprasidone is not marketed anywhere in the world at this time.

The following countries have approved the marketing of ziprasidone: Brazil (February 5, 1998), Sweden (as of June 10, 1998), Venezuela (November, 25, 1998), Czech Republic (March 15, 2000), New Zealand (April 20, 2000).

The sponsor listed the following countries where the application for ziprasidone is currently under review: Canada, Turkey, Malaysia, Hungary, South Africa, Switzerland, Egypt, Colombia, Slovakia, Poland, Croatia, Indonesia, Morocco, Slovenia, Mexico, and Bulgaria.

VI. Conclusions/Recommendations

This safety update includes ECG data from Study 054, which indicate that ziprasidone produces a QTc prolongation that is substantially greater than the other tested atypical antipsychotics and haloperidol, but less than thioridazine. The magnitude of the mean change from baseline of 20 msec is well above that suggested as the threshold for concern (5-10 msec) stated in our non-approvable letter of June 17, 1998.

The cardiac risks associated with QTc prolongation in antipsychotic drugs have been discussed in two open public discussions (PDAC: for sertindole and ziprasidone). Aside from the formal votes, there was an acknowledgement of the association of QTc prolongation with the events of syncope, ventricular arrhythmia, and sudden unexplained death; however, there has been a lack of sufficient evidence to directly address the safety risk associated with this degree of QTc prolongation. Hence, there was no data presented to suggest that our previous level of concern regarding the cardiac safety of ziprasidone, the sole determinant of the non-approvable action in 1998, was unwarranted.

The sponsor states that ziprasidone has advantages over other marketed antipsychotics such as less weight gain and a less adverse effect on lipid profiles. However, it is questionable if these advantages outweigh the cardiac risks of this drug, such as potentially fatal arrhythmias. Weight gain and lipid abnormalities can be detected early, monitored, and managed, unlike ventricular arrhythmias, which cannot be predicted and may have irreversible consequences.

After consideration of this safety update and the discussion of the ziprasidone PDAC, I must conclude that the extent of QTc prolongation associated with ziprasidone represent a signal of cardiac risks which do not outweigh the benefits of treatment. If the sponsor were able to demonstrate ziprasidone's ability to effectively treat patients with treatment refractory schizophrenia, then, perhaps for some individuals, this would offer an overriding benefit. Until there is evidence to support that advantage, it is recommended that this application not be approved.

S U — 7/28/00

Roberta L. Glass, M.D.
Medical Officer, Division of Neuropharmacological Drug Products

NDA 20-825
Div File
HFD-120:Katz/Laughren/Hardeman/Glass

8-9-00

I disagree with the above conclusion & recommendation. I feel that ziprasidone can be approved. The basis for this view is provided in a memo to the file on this date.

/S/ , MD
Team Leader, DPDRP

APPENDIX I

Deaths occurring during or after trial treatment : Cut-off date: 2/5/00

Ziprasidone subjects who died ≤ 30 days after treatment

SUBJECT #	AGE / SEX	LAST DOSE (MG/D)	DAYS OF TREAT-MENT	CAUSE OF DEATH/COMMENTS
108E-7160157**	49/M	160	466	Found unresponsive on bathroom floor immediately after a thump was heard. Was reported to have been revived for several minutes after brother administered CPR, but ECG showed asystole in emergency room. Lab tests showed CPK=851 IU(24-195 IU) with MB fraction of 6.0 ng/ml (0-5.0 ng/ml), potassium=6mEq/L(3.3-5.1 mEq/L), bicarbonate=10 mEq/L(24-32 mEq/L). Ziprasidone level (at death)=14 ng/ml. Investigator thought cause of death was acute myocardial infarction. No autopsy performed. No coroner's report available. ECGs during the study: Screening: QTc=432 Baseline: QTc=396 Week 6: QTc=396 Week 40: QTc=415 Was on ziprasidone at time of death.
Yale-9990040**	34/M	100	319	Found dead. Had complained of chest pain on the day of his death.. Had complaint of brief episodes of "heart pounding" and "skipping heartbeats" during the study. An autopsy report stated that the cause of death was occlusive coronary atherosclerosis. ECGs during the study: Screening: QTc=377 msec Wk1: QTc=413 Wk8: QTc=378 Wk24: QTc=391 Wk40:QTc=429 Wk2: QTc=390 Wk12:QTc=425 Wk28:QTc=390 (died during Wk45) Wk3: QTc=409 Wk16:QTc=366 Wk32:QTc=405 Wk4: QTc=397 Wk20:QTc=407 Wk36:QTc=397 Was on ziprasidone at the time of death.

*Included in Sudden Unexpected Death (SUD) rate calculation
*Reported after 8/29/97

Appendix I: Table of Deaths (con't)				
NY-97031E0054*•	51/M	40	151	Found dead. Two days prior to death, patient c/o not feeling well. Five days prior to death was seen by general practitioner with bp=140/100; no neurological findings noted. ECG at Day 7 showed flat T waves. ECGs during study: Screening: QT/QTc=358/428msec; HR=86bpm Wk1: " " =351/425 ; " =88 Wk6: " " =383/393 ; " =63 Wk13: " " =405/416 ; " =63 (patient died Wk21) According to sponsor, a discussion with medical examiner suggested left meningioma without evidence of brain injury was found on autopsy; however, no report available.
JP-96-602-450081*•	50/M	40	Unclear	Unknown cause of death. Baseline values: heart rate=46bpm; QT/QTc= 140/359 msec. One day after starting ziprasidone, patient presented at hospital with c/o palpitations and nausea; bp=150/100 mmHg, hr=119, QT/QTc=282/398. Two days after starting ziprasidone: ECG showed hr=47, QT/QTc=384/349; WBC=13130 cells/UL (NL: 3000-9000 cells/UL), neutrophils 81.4% (NL:40-74%), CPK=297 IU/I (NL:26-200 IU/I); diagnosed with URI and treated with antibiotic, flomoxef. Police contacted patient's physician to report his death; police ruled out suicide and homocide. **Death occurred within five days after starting ziprasidone (length of treatment unclear).**
105-5340021*	70/F	2	5	Patient had sudden onset of shallow respirations and diaphoresis. Death certificate stated acute cardiopulmonary arrest due to arteriosclerotic cardiovascular disease. Subject with history of right bundle branch block, otherwise ECG was normal. Was taking ziprasidone just prior to death.
108-6070305*	46/M	80	61	Found dead (in heat of 100°F). Autopsy report stated cause of death as acute and chromic asthmatic bronchitis and granulomatous myocarditis. ECG: Screening: QTc =366 msec Baseline: QTc =393 Week 6: QTc=395 Was on ziprasidone at time of death.
108-5920750*	39/F	120	8	Found dead one day after her estimated date of death of unknown cause. Patient's face was burned and it was thought that she had fallen against a hot water pipe. The investigator's postmortem diagnosis was alcohol abuse/diabetic ketoacidosis, but there is no evidence for this. No coroner's report located in the CRF. Was on ziprasidone at time of death.

*Included in Sudden Unexpected Death (SUD) rate calculation
•Reported after 8/29/97

Appendix I: Table of Deaths (con't)				
116B-5080001*	54/M	120	71	Found dead in his hospital bed. Autopsy showed generalized atherosclerosis, coronary artery disease, cerebral artery disease, visceral congestion (liver, spleen, and lung), COPD, and cardiac hypertrophy. ECGs during the study: Screening: QTc=391 msec baseline: QTc=383 week 2: QTc=367 week 6:QTc=391 Patient had complaint of chest pain once during the study, but ECG was normal and diagnosed as anxiety. Was on ziprasidone at time of death.
302E-3190375*	48/M	120	162	Found dead. CRF showed hypertension and tachycardia on last day of study with hypertension as adverse event during study. Narrative states that subject had history of polydipsia and seizure disorder. Details regarding the death are unclear. Died one day after discontinuing ziprasidone.
304E-1930379*	52/M	80	221	Found dead while taking a nap. No autopsy performed and exact cause of death is unknown. ECG during the study as shown in the safety update: QTc at: Screening=374.7 msec Week 12=415.69 Week 28=413.12 with flat T wave in lead AVL; no evidence of ischemic changes. The CRF had minimal information and the patient profile in the safety update had different ECG QTc values than the original submission. Was on ziprasidone at time of death.
301-311-0977*	28/F	120	57	Patient reported be cachectic and had ECG changes consistent with subendocardial ischemia with substernal pinching sensation. Patient was d/ced from ziprasidone and treated with thioridazine, nitrazepam and patient died two days later. Cause of death reported to be myocarditis. Death occurred 2 days after d/c from ziprasidone.
308-0350003	63/M	80	485	Sudden collapse and died. Coroner's report stated that cause was a ruptured abdominal aortic aneurysm and atherosclerosis. Was on ziprasidone at the time of death.
115-6940394	43/M	40	16	Found dead. Coroner's cause of death listed as asphyxiation due to aspiration of vomit . Was on risperidone, clonazepam and lorazepam at time of death. Patient had difficulty breathing three days before death, and complained of dyspnea on morning of death. Died 29 days after discontinuing ziprasidone.

*Included in Sudden Unexpected Death (SUD) rate calculation
*Reported after 8/29/97

Appendix I: Table of Deaths (con't)				
116B-6590001	44/F	120	47	Patient had a UTI upon d/c and was diagnosed with gastritis with Helicobacter pylori 13 days later. She was seen in ER with diagnosis of panic attack 21 days after d/c (three days prior to death). Sponsor reports that the autopsy was not available due to legal issues in medical examiners, but Subject's attending physician reportedly got information from the medical examiners that subject had a benign cardiac neoplasm (myxoma).ECG: screening: QTc=444 msec baseline: QTc=443 week 1: QTc=433 week 2: QTc=440 week 6: QTc=407 Patient reported chest pain one day after starting ziprasidone: cardiology w/u was normal, but had elevated transaminases. Episodes of tachycardia and hypertension during the study: day 6:102 bpm day 20:120/100; 104 bpm day 27:140/100; 102 bpm day 42:164/98 It is unclear what medications she was on as the patient summary and the CRF do not list the same medications. **Death occurred 24 days after d/c from ziprasidone.**
303-1970299	79/F	80	30	Cardiac arrest. No autopsy was performed. Patient had new diagnosis of atrial fibrillation and ischemic heart disease 27 days after d/c. At time of death was taking perphenazine, deparkin, digoxin, verapamil, and enalapril. **Death occurred 30 days after d/c from ziprasidone.**
Suicides and accidents				
108-6090381	21/F	160	54	Suicide by gunshot while on ziprasidone.
116B-6940004	24/M	160	146	Suicide by hanging while on ziprasidone. Subject had been complaining of increasing depressed mood; treatment included an increase in ziprasidone.
117-6870317	51/M	120	205	Death by defenestration. According to study profile, patient did not appear suicidal prior to death.
117-7060529	40/M	160	54	Patient stopped ziprasidone on his own and four days later he drove his car off a cliff. Subject was driving his car after a sleep deprived EEG against medical advice. Autopsy listed asphyxiation due to drowning and was classified as a probable traffic accident.
302-2600156	46/M	120	7	Patient's body found drowned in local river after being missing from the hospital for five days.
302E-1590029	22/M	120	179	Suicide by falling under a train. Was being treated with ziprasidone at time of suicide with plans to be admitted to the hospital that same day.
JP-95-6011622	53/M	53	20	Suicide seventeen days after discontinuing ziprasidone (Japanese studies: not part of the integrated safety data base.)
NY-97-002-0022*	34	160	9	Probable suicide by drowning. Was on ziprasidone at time of death. Postmortem finding reported pulmonary congestion and pulmonary edema consistent with drowning episode as cause of death.
NY-97-002-0077*	37	60	13	Died of carbon monoxide poisoning and cardio-respiratory arrest secondary to accidental fire, according to coroner's report. Patient found unconscious. Was on ziprasidone at time of death.
NY-97-033-053 *	23	160	53	Suicide by gunshot while on ziprasidone

*Included in Sudden Unexpected Death (SUD) rate calculation
*Reported after 8/29/97

Appendix I: Table of Deaths (con't)				
NY-97-033-266*	20	160	8	Drowned while swimming in the sea. Patient had c/o palpitations for 4 months prior to death; also c/o dystonia 4 days prior to death, treated with trihexyphenidyl and benztropine, and was on propranolol. On ziprasidone at time of death.
601E-0187-0118*	41	80	46	Probable suicide; autopsy report states cause of death: exsanguination from multiple deep incised wounds. On ziprasidone at time of death.
R0553012097-R0267*	47	80	19	Suicide by hanging. Was on ziprasidone at time of death.

Ziprasidone subjects who died ≥ 30 days after treatment

SUBJECT #	AGE/ SEX	DOSE (MG/D)	DURATION (DAYS)	CAUSE OF DEATH
104-5130213	40/M	40	28	Sudden death; cause unknown. Occurred 7½ months after discontinuation from ziprasidone .
106-05550117	35/M	40	27	Unknown cause of death but possible seizure and aspiration of vomit. Was taking risperidone at time of death. Death occurred 4½ months after stopping ziprasidone .
108-5780020	37/M	80	8	Accidental drowning. Died 1½ months after stopping ziprasidone .
117-6940542	38/M	160	15	Suicide by gun shot one year after d/c from ziprasidone .
127E-06810002*	25/M	160	185	Died of lobar pneumonia 2 months after stopping ziprasidone. IM:po extension study.
127E-07190004*	48/F	120	164	Died of unknown causes over 2 months after stopping ziprasidone.
301-1140331	30/M	200	26	Died of complication due to pancreatitis 9 months after stopping ziprasidone
301-1320771	34/M	120	53	Suicide by hanging approximately 3 months after stopping ziprasidone .
303-0640276	61/M	40	69	Died of bronchopneumonia with bronchial adenocarcinoma and metastasis. Death occurred 4 months after stopping ziprasidone.
303-1950250	68/M	40	350	Died of cranial trauma 2° to fall. Ziprasidone was stopped 45 days prior to death.
303-1950256*	68/F	80	63	Died of heart failure more than 2 years after stopping ziprasidone.
303-1950281	71/F	40	61	Sudden death due to acute purulent leptomeningitis. Death occurred 4 ½ months after stopping ziprasidone.
303-1970269	67/F	80	37	Bronchopneumonia. Stopped ziprasidone112 days before diagnosis.
303-1990089 no CRF available	55/M	80	27	Sudden death due to acute cerebral edema. death occurred 60 days after stopping ziprasidone.
303-2120222	58/M	160	349	Died of post operative cerebral edema after tumor removal. Occurred two months after stopping ziprasidone

*Included in Sudden Unexpected Death (SUD) rate calculation
*Reported after 8/29/97

Appendix I: Table of Deaths (con't)

304-2040222	55/F	160	29	Sudden death with proposed cause of acute heart failure due to pulmonary disease. Death occurred approximately 2 months after stopping ziprasidone.
307-2650034*	47/M	80	365	Death from trauma of fall from window over one year after discontinuing ziprasidone.
307-2690047	49/F	100	196	Died of hepatic coma, cholestatic jaundice and malignant neoplasm 95 days after stopping ziprasidone. Discontinued ziprasidone because of jaundice and elevated AST (244 U/L) and ALT (375 U/L).
NY-97-001-355*	25/M	160	41	Suicide by hanging 2 months after stopping ziprasidone. IM/po extension study.
NY-98-035-0572*	23	160	71	Suicide by hanging 6 weeks after stopping ziprasidone. IM/po extension study.
NY-98-035-586*	30/M	160	60	Died of pneumonia 33 days after stopping ziprasidone.
JP-94-601 0014*	51/F	20	37	Died of myocardial infarction. Symptoms began 6 days after d/c from ziprasidone when patient fell, diagnosed with cyanosis requiring oxygen therapy. Fifty-five days, later patient died. During study ECGs were read as abnormal as follows: Baseline: ST-T Abnormal Wk8: ST-T Abnormal Follow Up: ST-T Abnormal Wk4:ST-T Abnormal Right Atrial Hypertrophy Right Atrial Hypertrophy Right Atrial Hypertrophy Sinus Tachycardia

*Included in Sudden Unexpected Death (SUD) rate calculation
*Reported after 8/29/97

APPENDIX II

Other Overdose Cases During Treatment with Ziprasidone

3083200008	36/F	Unknown		Randomized to ziprasidone group. Patient reported to have ingested alcohol and taken O/D of risperidone. Had postural hypotension and lengthening of QTc (centrally read): Baseline QTc=413; On day of event: QTc=458.
1085230870	41/M	Unknown		Patient reporting taking O/D of diazepam and lorazepam to self treat insomnia.
1085820420	35/M	Unknown		Patient found comatose and thought to have overdosed. Responded to naloxone with improved respiration. Drug screen positive for propylene glycol, cocaine & opiate. Lithium level=0.5 mEq/L; ziprasidone serum concentration < 1ng/ml (below limit of quantization). Treated with gastric lavage and charcoal. Many complications during course of treatment (see 4/6/00 submission for details).
116B5510005	38/M	Unknown	Aspirin	Patient reported O/D of aspirin. ECG was WNL; blood gas showed respiratory alkalosis and metabolic acidosis. Recovered in 24 hours.
116B5553002	62/F	Unknown	Thioridizine	Patient admitted to hospital for sedation and discharged 12 days later. Narrative suggests possible O/D of thioridizine, but this is unclear.
116B5810014	35/F	Unknown	Lorazepam	Patient reported O/D of lorazepam. Gastric lavage performed.
116B5950018	33/F	Unknown	Lorazepam flurazepam	Staff reported O/D of lorazepam and flurazepam
116B6690025	41/F	Unknown	Acetominophen	Patient reported O/D of acetominophen and drinking alcohol. No symptoms reported.
1175080352	54/M	Unknown	Chloral hydrate Lorazepam	Found on floor. Thought to be intentional overdose of chloral hydrate and lorazepam. L Treated with activated charcoal; rhabdomyolysis in leg.
3011110384	28/F	Unknown		Patient reported O/D on cyamemazine with recovery after gastric lavage.
3011320771	34/M	Unknown		Reported as suicide attempt by poisoning. No details located.
3011380814	27/M	Unknown	Temazepam	Report to have ingested zopiclone; hospitalized and recovered after gastric lavage.
3021500046	18/M	Unknown		Reported to have ingested haloperidol. Hospitalized and received gastric lavage.
3040390343	27/F	Unknown		Reported to have ingested O/D of aspirin.
3041720304	24/M	Unknown	Parcetamol lorazepam	O/D of lorazepam.
601E1920034	40/F	Unknown	Lorazepam	O/D of lorazepam to treat insomnia. Patient hospitalized for confusion, disorganized thoughts and bizarre behavior.
R5550007	19/M	Unknown		Excessive alcohol intake reported. Event resolved 4 days later.
NY980350474	?/F	Unknown		Reported to have taken O/D of zopiclone.
980350338	33/M	Unknown		Reported to have taken O/D of zolpidem & chlordiazepoxide.

APPENDIX III SERIOUS ADVERSE EVENTS FOR ZIPRASIDONE GROUPS Period of May 15, 1997 to February 5, 2000 (table revised from sponsor's submission of 5/22/00)	
PID	**Event**
Cardiovascular	
302E-057-0456	Syncope and bradycardia
127E-595-0013	Bradycardia (2 episodes)
127E-701-0003	Cardiomegaly; Possible Congestive Heart Failure; Pneumonia
R-0554-0070	Congestive Heart Failure; Chronic Obstructive Pulmonary Disease
303-269-0207	Hypertension
308-320-0008	Prolonged QT Interval; Worsening Schizophrenia
NY-97-014 252	Convulsion; Prolonged QT Interval
R-0554-0129	Arterial Occlusion; Leg Amputation
JP-96-602 460001-1	Cerebral Infarction
Seizure	
123-1001-0061	Recurrence of Tonic-Clonic Seizure
127E-795-0002	Seizure
NY-97-O31E 0033	Generalized Tonic-Clonic Seizure
601E-0624-0123	Seizure
602-0651-0105 (also listed as 602-216-0105)	Tonic-Clonic Seizure
R-0554-0126	Grand Mal Seizure
NY-97-014 252	Convulsion; Prolonged QT Interval
Movement Disorders	
116B-0581-0017	Exacerbation of Tardive Dyskinesia
108E-0523-0148	Left Leg Dystonia; Gait Disturbance
R-0554-012	Restlessness; Abnormal Movements of Lower Extremities; Tightness in Chest; Anxiety
R-0553-0045	Acute Dystonia
Possible NMS	
601E-0756-0085 (aka 69202190080)	Medication of induced movement disorder (NMS Like); Bipolar disorder, recurrent depression; respiratory distress; aspiration pneumonia
JP-95-601 57-2	Decreased Level of Consciousness; Hyponatremia; Increased Blood Pressure; Increased Heart Rate; Increased Creatine Phosphokinase
Metabolic/Hematologic	
JP-96-602 20601-1	Elevated Blood Sugar
R-0553-0201	Hyperglycemia
601E-0540-0077	Neutropenia
NY-97-014 052	Dizziness; Unstable Balance; Falls; Shallow Respirations; Decreased Hemoglobin; Increased Platelets; Unsteadiness in Feet; Oculogyric Crisis; Extrasystoles; Postural Hypotension
Skin	
108-0681-0618	Cellulitis, Facial
116B-0590-0003	Cellulitis
108E-0509-0168	Ulcerated Basal Cell Carcinoma
NY-97-031 0041	Cellutitis
307-0265-0035	Sunburn

Pulmonary	
108E-0594-0094	Aspiration of Food
R-0553-0083	Pulmonary Emboli
R-0553-0160	Pneumonia; Worsening of Schizoaffective Disorder
127E-595-0016 127E-669-0008	Exacerbation of Asthma; Exacerbation of Schizophrenia Traumatic Pneumonthorax,
NY-98-035 0585	Left Lower Lobe Pneumonia; Pneumothorax
601E-0627-0070	Right Lower Lobe Pneumonia
Gastrointestinal	
NY-98-035 0246	Nausea; Serious Diarrhea
116B-0596-0006	Worsening of Gastroesphogeal Reflux Disorder; Barrett's Esophagitis; Laparoscopy with partial Fundoplication
116B-0556-0001	Worsening Diverculosis
601-0540-0217	Worsening Gastric Erosion; Worsening Duodenitis; Exacerbation of Bipolar Disorder, Mania
Miscellaneous	
602E-0651-0084 (Previously listed as 602E-0246-0084)	Excessive Sedation
108E-0620-0041	Papilloma, left Ureter; Transitional Cell Carcinoma in Situ, Left Ureter
R-0553-0191	Breast Cancer - Female
601E-0756-0086	Carcinoma of the Bladder, Deep Vein Thrombosis
NY-98-035 0576	Tonsillitis
Fractures	
1160-603-0002	Open Reduction Internal Fixation of Right Humerus
116B-0523-0002	Fractured Femur, Accidental
116S-0653-0003	Ankle Fracture; Accidental
168E-0881-0079	Surgical Site Infection, Right Foot
127E-719-0005	Ankle Fracture, Accidental; Staphylococcus Infection; Increased Depression
JP-96-602 270050-4	Accidental Bone Fracture
R-0554-0024	Fractured Ankle
Exacerbation of Psychiatric Illness and Suicidal Gestures	
116B-0551-0002	Exacerbation of Schizophrenia; Recurrent Depression; Suicidal Gesture
116S-0650-0001	Exacerbation of Chronic Paranoid Schizophrenia
108E-0523-0203	Exacerbation of Psychotic Symptoms; Suicidal Ideation; Increased Insomnia
116B-0581-0014	Suicide Attempt; Intentional Drug Overdose; Persistent Depression
116B-717-0003	Exacerbation of Schizophrenia
R-0554-0050	Exacerbation of Psychosis; Attempted Suicide (Laceration of Wrist)
JP-95-601 131-2	Exacerbation of Schizophrenia; Suicide Attempt
301E-0102-0231	Alcohol Intoxication; Alprazolam Intoxication
NY-97-031E 0016	Suicidal Ideation
NY-97-032 020	Relapse of Schizophrenia; Manic Seizure
NY-97-033 288	Exacerbation of Psychosis
NY-98-035 0025	Suicide Attempt
NY-98-035 0043	Exacerbation of Schizophrenic Symptoms; Manic Episodes; Zona (Herpes Zester)
NY-98-035 0058	Psychotic Relapse
NY-98-035 0079	Increased Irritability; Anxiety, Lesions on Hands; Possible Hallucinations; Exacerbation of Psychosis

NY-98-035 0093	Exacerbation of Schizophrenia
NY-98-035 0518	Worsening Psychosis
NY-98-035 218	Suicide Attempt (Laceration of Wrists)
NY-98-035 0255	Suicide Attempt; Worsening Hallucinations
NY-98-035-0923	Suicide Attempt By Jumping from window; fractured Clavicle; Brain Contusion
601-0615-0120	Exacerbation of Bipolar Disorder, Mania; Exacerbation of Bipolar Disorder, Depression; Suicidal Gesture
601E-0669-0021	Suicidal gesture; Exacerbation of bipolar disorder, depression
601E-0529-0176	Exacerbation of Bipolar Disorder, Depression; Suicidal Ideation
601E-0646-0059 (Previously listed as 601 E-0201-0059)	Anxiety
601E-0279-0319	Recurrent Suicide Attempt
602E-0719-0123	Exacerbation of Mania
602E*0662-0051 (Previously listed as 602E-0244-0051)	Exacerbation of Mania
602E-0662-0125	Exacerbation of Bipolar Disorder, Mania
602E-0764-0062 (Previously listed as 602E-0255-0062)	Bipolar Disorder, Recurrent Depression; Suicidal Ideation
R-0554-0061	Worsening Psychosis; Suicide Attempt
R-0555-6039	Suicide Attempt
R-0585-6061	Exacerbation of Psychosis

APPENDIX IV

Reasons for Discontinuations For Period of May 15, 1997 to February 5, 2000

Nausea, vomiting, chest pain, headache, dizziness, hypertension, tardive dyskinesia, cerebrovascular accident, dystonias, tic disorder, EPS, akathisia, tardive dyskinesia, excessive weight loss, increased liver function test (alkaline phosphatase, SGPT, SGOT), somnolence, bradycardia, impotence, convulsion, ataxia, multiple sclerosis, insomnia, leg cramps, pancreatic cancer, tuberculosis, hepatic metastases, orthostasis, bronchospasm, meningitis, billiary tract disorder, catatonia, mania, sweating, anxiety, gynocomastia, and anemia.

#1

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA 20-825
Sponsor: Pfizer Inc.
Original User Fee Due Date: March 17, 1998
Extended User Fee Due Date: June 17, 1998

Drug Name

Generic Name: Ziprasidone hydrochloride
Trade Name:

Drug Characterization

Pharmacologic Category: Serotonin and Dopamine Antagonist
Proposed Indication: Management of the Manifestations of Psychotic Disorders
NDA Classification: 1S
Dosage Forms: Oral tablets; 20, 40, 60, 80 mg capsules

Reviewer Information

Clinical Reviewer: Roberta L. Glass, M.D.
Review Completion Date: April 30, 1998

Table of Contents for Clinical Review of NDA 20-825

7.0 Review of Efficacy

8.0 Integrated Review of Safety

1.0 Material Utilized in Review

1.1 Material from NDA/IND

This NDA submission was presented in a combination of hard copy and electronic format. Case report forms were submitted in electronic format only. Addendum submissions clarifying issues of the original submission (3/18/97) were in hard copy only except for the safety update (8/29/97) which was submitted in both hard copy electronic format . There were no electronic datasets provided for this review.

The documents most frequently referred to for the purposes of this review were the following:

Integrated summary of efficacy
Integrated summary of safety
Study reports for trials 104, 106, 114, 115, and 303
Safety update report of 8/29/97
Literature summary

Also considered were Pfizer's commercial IND(for agitated psychotic subjects) and IND( )(ziprasidone po for mania).

Case report forms were examined for the following subjects: all reported deaths, 116B-5510007,303-1970265, 303-0070098, 109-5720027, 117-6200029, 108-5740080, 114-6560036, 116B-551-0008, 303-2120105, 303-1970265, 102-5130005, 108-5740080, 109-5650041, 303-2710228, 116B-05230001, 304-1890367, 108-6170817, 117-7060373, 117-7060380, 115-06560036.

1.2 Related Reviews and Consults for the NDA

The Division of Cardio-Renal Drug Products was consulted for issues concerning ziprasidone's prolongation of the QTc interval on ECG recordings by Charles J. Ganley(HFD-110: 11/18/98 and 1/6/98). Also referred to were the following reports: 1) *A Review of UK Post-Marketing Surveillance Experience with Sertindole, Olanzapine and Risperidone* by Greg Burkhart, M.D., M.S. (HFD-120: 12/12/97), 2) Clinical Pharmacology and Biopharmaceutics Review by Sayed Al-Habet, Ph.D. (HFD-860: 3/3/98), 3) Review of Clinical Data: *General Characteristics of the Deaths in the NDAs for Olanzapine, Risperidone, Quetiapine and Sertindole* by Greg Burkhart, M.D. (HFD-120: 3/3/98), 4) Review of Data Quality, Coding, All Cause Mortality and Sudden Deaths by Gerard Boehm, M.D., M.P.H. & James F. Knudsen, M.D., Ph.D. (HFD-120: 2/3/98), 5) Review of Ziprasidone ECG Data by Gerard Boehm, M.D., M.P.H. (HFD-120: 1/23/98), and 6) Statistical Review and Evaluation by Sue-Jane Wang, Ph.D. (HFD-710: 11/24/98).

1.3 Other Resources

Dr. Andrew Mosholder provided excellent mentoring in the preparation of this document and throughout the review process.

2.0 Background

2.1 Indication

The majority of the fifteen medications currently labeled for the indication of psychosis are considered to be traditional dopamine antagonist agents. These traditional agents have been associated with a high incidence of extrapyramidal symptoms (EPS) and long term risks of tardive dyskinesia. The more recently marketed 'atypical' antipsychotic agents (clozapine, risperidone, olanzapine, and quetiapine) possess serotonin type 2 ($5\text{-}HT_2$) receptor blocking activity in addition to their dopamine antagonist properties. It has been suggested that these 'atypical' agents may reduce the incidence of EPS, result in less risk of the

development of tardive dyskinesia, and be more effective in treating the negative symptoms of schizophrenia. In light of the risks of agranulocytosis associated with clozapine, it is indicated only for refractory patients. Of these 'atypical' antipsychotic drugs, only clozapine has shown superior efficacy in refractory patients thus far.

The sponsor of ziprasidone has characterized this drug as an 'atypical' antipsychotic demonstrating dopamine and serotonin receptor antagonist activity. The sponsor proposes that this medication minimizes EPS and also treats both positive and negative symptoms of schizophrenia.

The NDA for another 'atypical' neuroleptic, sertindole, was recently withdrawn because of concerns about QT interval prolongation and sudden deaths.

2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

Pfizer has submitted IND( ). This sponsor also submitted IND( ) to study ( ). The review for these other submissions are still in progress and will not be discussed in this review except for relevant safety data.

According to a teleconference of September 4, 1997 with Dr. Ritrovato from Pfizer, all clinical studies of ziprasidone have been done under Pfizer's sponsorship.

In a recently reviewed NDA for the 'atypical' antipsychotic sertindole, concerns arose regarding the high incidence of sudden death and prolongation of the QTc interval within this NDA safety data base. In the literature there have been observations that QTc prolongation may be correlated with the development of ventricular arrhythmia, syncope, and sudden death (Morganroth, 1993). This safety concern was intensified when post marketing data from the U.K. were reviewed by Greg Burkhart, M.D., MPH (12/12/97), and it was found that sertindole demonstrated a higher sudden unexplained death reporting rate than olanzapine and risperidone. The sponsor of sertindole withdrew this NDA.

2.3 Administrative History

The original commercial IND for oral ziprasidone was filed on April 3, 1990. FDA allowed women of child bearing potential to be included in clinical trials in October, 1991; the sponsor began to include women of child bearing potential in August, 1993.

An End of Phase II meeting between FDA and the sponsor was held in March 1994. At that time, the FDA requested that the sponsor repeat the Segment II study in rabbits because of the low survival rate of fetuses and the lack of skeletal and visceral examination in all fetuses. FDA also requested that if the sponsor was interested in correlating neoplastic changes in pre-clinical carcinogenicity studies to an increase in serum prolactin, they would need to document that serum prolactin levels were simultaneously elevated in these animal studies. Characterizing the pharmacokinetic characteristics of ziprasidone and its metabolites was also emphasized.

According to FDA records, a pre-NDA meeting was held in May, 1996. During this meeting, the pharmacology group requested that the sponsor submit separate tables describing neoplastic and non-neoplastic findings from rat carcinogenicity studies; it was again requested that the sponsor submit pre-clinical data characterizing ziprasidone's effect on serum prolactin concentration and its relationship to neoplastic changes. The sponsor was also encouraged to identify the metabolic pathway of ziprasidone and cytochrome characterization to develop information regarding drug interactions. The format for the NDA submission was discussed during the pre-NDA meeting.

In July 1996, the sponsor met with the FDA to discuss and demonstrate the electronic submission of the NDA. In September, 1996, Pfizer was granted a waiver for submitting the case report forms in hard copy.

In November 1996, the sponsor met with the FDA chemistry group to discuss issues regarding chemistry, manufacturing and controls.

The original NDA was submitted to FDA on March 18, 1997 with a cut-off date listed as October 31, 1996. A safety update was submitted by the sponsor on August 29. 1997 with a cut-off date recorded at May 15, 1997.

In October 1997, the Division notified the sponsor by letter that there were concerns regarding the finding of QT interval prolongation with the use of ziprasidone.

On December 16, 1997, the sponsor notified DNDP that they intended to submit a major amendment to the NDA which would subsequently entitle the sponsor to have a 3 month user fee extension; this amendment (submitted 1/23/98) included one pre-clinical study and data from two pediatric studies (one completed study with n=18 and one interim report) in children with Tourette's Syndrome.

2.4 Proposed Labeling

The dosing instructions in the draft labeling recommended an initial dose of 40 mg bid with food, and, if needed, followed by dose titration up to 80 mg bid at intervals of 2 days or more. The labeling states that doses above 80 mg bid were not shown to be more efficacious than 80 mg bid, and that clinical assessment is recommended if a dose greater than 80 mg bid is to be undertaken. It is also mentioned that the safety profile of doses above 100 mg bid have not been assessed.

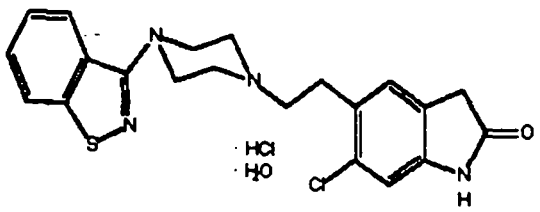
For maintenance therapy, the draft labeling recommends that the dose be 40 mg bid with allowance for individual patient differences. There is no maximum time period stated for use. It also states that no dose adjustments are necessary for age, gender, race, renal or hepatic impairment.

2.5 Foreign Marketing

Ziprasidone is not marketed anywhere in the world.

3.0 Chemistry, Manufacturing and Controls

The chemical structure for ziprasidone is:



4.0 Animal Pharmacology and Toxicology

In vitro studies have shown that ziprasidone is a serotonin (5-HT_{2A})and dopamine type 2 (D_2) antagonist. Other receptor effects of ziprasidone include histamine (H_1), α_1 adrenergic, 5-HT_{1A} (agonist), $5HT_{1D}$ (antagonist), and $5HT_{2C}$ (antagonist) receptor affinity. There is evidence that ziprasidone blocks neuronal reuptake of serotonin and norepinephrine, and inhibits the contractile effect of norepinephrine on guinea pig aortic strips.

In animal models, ziprasidone demonstrated potential for antipsychotic properties. The suggestion that it would have less severe motor side effects than traditional antipsychotics was supported by its weak ability to induce catalepsy in animals; its potential to treat negative symptoms was theoretically demonstrated in its ability to increase the release of dopamine in rat prefrontal cortex.

Reproductive studies in rabbits resulted in decreased birth weight, decreased birth survival, decreased maternal weight gain, decrease in the number of viable litters, and abnormal fetal heart development. Ziprasidone has been shown to exhibit placental transfer in rats and rabbits. In chronic toxicology studies, sedation and reduced body weight gain were observed in rats and dogs. Also observed in dogs were motor side effects, and intrahepatic cholestasis (correlated with increases in ALT and alkaline phosphatase).

The mouse carcinogenicity studies showed dose related increases in the incidence of pituitary adenomas and mammary gland adenocarcinomas.

In the opinion of FDA consultants, the safety preclinical pharmacology evaluation of the original NDA submission did not include an adequate work up of ziprasidone's effect on the QT interval.

In a meeting package (2/13/98), the sponsor concluded that ziprasidone and the metabolite ziprasidone-sulfoxide did not demonstrate significant effects on the action potentials of Purkinje fibers in dogs; FDA cardiology consultants (HFD-110) expressed concern that the sponsor did not test a high enough concentration of ziprasidone in this study to fully characterize the effects of ziprasidone in the therapeutic dosage range (note: the sponsor has not submitted a study report for review). In a meeting with FDA and the sponsor (3/27/98), the sponsor presented a brief summary of data which suggested that ziprasidone may inhibit the IKr channel, an ion channel implicated in the process of QTc prolongation (no data was submitted for review).

5.0 Description of Clinical Data Sources

5.1 Primary Source Data (Development Program)

5.1.1 Study Type and Design/Patient Enumeration

The sponsor submitted three different calculations to characterize the subject exposure history of ziprasidone, and there was some discrepancy amongst the tables presented by the sponsor; this review will attempt to clarify these submissions. The following table (adapted from the sponsor's submission of 3/20/98) gives a summary of person time in the ziprasidone safety data base:

Subject-years exposure in ziprasidone safety data base*

ORIGINAL NDA	ZIPRASIDONE	PLACEBO	HALOPERIDOL	RISPERIDONE
N=	2163*	366	407	206
Subject-years exposure*	626*	51	86	84
SAFETY UPDATE				
N=	2588	382	585	295
Subject-years exposure*	772	52	131	105
REPORT of 12/31/98				
N=	2993	424	653	298
Subject-years exposure*	1189	82	228	155

*** Includes Studies 105 and 120 which were not in the integrated safety data base.(see below for details)**

Discrepancies in the total number of subjects exposed is explained by the fact that the sponsor did not consistently exclude or include studies 105 (11 elderly demented subjects) and study 120 (12 psychotic subject taking the IM formulation). Studies 105 and 120 were not included in the integrated safety data base. Therefore, in the original submission (submitted: 3/18/97;cut off date: 10/31/96), there were actually a total of **2140** subjects enrolled in phase II/III oral ziprasidone studies in the integrated safety data base. This is the number of subjects upon which the demographic characteristics presented below (section 5.1.2) is based.

Appendix Table 5.1.1.1 lists the cumulative number of subjects in the original integrated safety data base and the safety update with a cut-off date of May 15, 1997. The safety data base (submission of 8/29/97) for Phase I, II, and III of ziprasidone trials included a total of 3318 subjects exposed to ziprasidone. There were 742 subjects in Phase I studies and 2565 subjects in the Phases II/III studies; this doesn't include study 105 in which 11 elderly subjects with dementia were exposed to oral ziprasidone. One other trial (study 120) for the IM formulation with 12 subjects was included in the enumeration of subjects in the original submission, but the sponsor did not include this data in the integrated safety data base for the oral ziprasidone NDA.

Please refer to Appendix 5.1.1.2 for a listing of all studies. The integrated safety data base encompasses 29 Phase II/III studies. The majority of subjects were enrolled in controlled studies.

5.1.2 Demographics

Please refer to Appendix 5.1.2.1 for a demographic profile of all Phase I studies. The sponsor did not recalculate demographics based on the additional information in the safety update for phase I trials.

All demographic information for the cumulative Phase II/III safety data base as of 8/29/97 can be found in Appendix 5.1.2.2.

These tables show that the majority of subjects in Phases I and II/III were Caucasian males between the ages of 18-64 years old.

5.1.3 Extent of Exposure (dose/duration)

The modal daily dose and duration for Phase I studies are shown in Appendix 5.1.3.1 (note: these figures are based on the original submission; the sponsor did not provide additional information in the safety update for phase I trials). This table reflects that the majority of subjects were exposed to low doses (< 100 mg daily) for less than 30 days which is not unusual for Phase I studies.

Appendix 5.1.3.2 is a table of the mean daily dose and duration during all oral dosing in Phase II/III studies (including data from the safety update of 9/29/97). There have been 1686 subjects (65.7%) within this pool who have been exposed to ziprasidone in the dosage range of 80 to 160 mg daily which is the recommended dose in the proposed labeling. There were 533 subjects (20.8%) exposed to ziprasidone for six months or longer. The following table (adapted from the sponsor's safety update, and presented above) gives a summary of person time in the ziprasidone safety data base:

Subject-years exposure in ziprasidone safety data base

ORIGINAL NDA	ZIPRASIDONE	PLACEBO	HALOPERIDOL	RISPERIDONE
N=	2163	366	407	206
Subject-years exposure*	626	51	86	84
SAFETY UPDATE				
N=	2588	382	585	295
Subject-years exposure*	772	52	131	105

REPORT of 12/31/98				
N=	2993	424	653	298
Subject-years exposure*	1189	82	228	155

* Includes Studies 105 and 120 which were not in the integrated safety data base.(see Section 5.1.1 for details)

The sponsor recorded the cut off date as 10/31/98 for the original submission . The cut-off date for the safety update calculations (submitted 8/29/97) was not made clear by the sponsor despite requests to do so. The sponsor reported that the subject-years exposure calculations for the REPORT of 12/31/98 was 12/31/98.

Please note that the sponsor included subjects from blinded groups to calculate the subject-years exposure; they did not explain their procedure despite requests to do so.

5.2 Secondary Source Data

5.2.1 Other Studies

The studies conducted in Japan were not included in the integrated summary data base, but safety data including discontinuations, adverse events, and laboratory test abnormalities was included in this submission. The cut-off date, including the safety update, is May 15, 1997. The Japanese studies include the following:

Phase I Studies (n= ziprasidone exposure)
93-501 (n=13)
93-502 (n=8)
93-503 (n=6)
93-504 (n=10)
94-501 (n=6)
96-501 (n=25)

Phase II Studies
94-601 (n=49)
95-601 (n=84)

The eight Phase I and three Phase II Japanese trials included 201 subjects as of the safety update of May 15, 1997 who were exposed to ziprasidone; the sponsor calculated that this represents 14.8 subject-years exposure.

5.2.2 Postmarketing Experience

As of September 4, 1997, Ziprasidone is not marketed in any country as per a teleconference with Dr. Ritrovato at Pfizer.

5.2.3 Literature

According to a teleconference of September 4, 1997 with Dr. Ritrovato from Pfizer, all clinical studies have been done under Pfizer's sponsorship and are included in the current NDA submission.

The sponsor has submitted nineteen published papers and abstracts (NDA Vol. 153 and 154) that either focused on or contained new information about ziprasidone. Publications which make only a reference to ziprasidone were not submitted; the cut-off for the bibliography was listed as October 31, 1996. The literature search was conducted by David L. Larson, Ph.D. who has been employed at Pfizer since 1971.

Of note in this literature review, there were two studies (Bench, 1996; Bench, 1993) which reported large elevations of prolactin levels when comparing baseline and peak plasma levels of ziprasidone in twelve normal volunteers taking between 5 and 60 mg of a single dose of ziprasidone.

Otherwise, my review of the sponsor's literature search did not reveal any unexpected safety findings.

6.0 Human Pharmacokinetic Considerations

For complete details, please refer to the biopharmaceutics review.

Oral ziprasidone is absorbed up to 100 % when administered in the fed state. In the fed state, the mean half-life is 6.6 hours (variability ranging from 3 to 18 hours) and a steady state is achieved within 1 to 3 days. In addition to increasing the AUC and Cmax, food was found to delay the Cmax and decrease the half-life by approximately 4 hours. Ziprasidone is highly protein bound with an absolute bioavailability of 60 % in the fed state. The mean volume of distribution is approximately 1.5 L/kg with a mean systemic clearance of approximately 7.5 ml/min/kg. Ziprasidone demonstrates linear kinetics in the fasting state. In an interim report of study 044, a single dose pharmacokinetic study in 15 pediatric subjects with Tourette's Syndrome (ages 7-16; n=15), preliminary finding showed that the half-life range was 3.3-4.7 hours (note: an oral suspension of 40 mg/ml was used in study 044).

The major metabolites identified are ziprasidone-sulfoxide and ziprasidone-sulfone; both demonstrate a low affinity to D_2 and $5HT_{2A}$ receptors. In vitro studies of human liver microsomes suggest that ziprasidone is a cytochrome P450 3A4 substrate mainly for the metabolic processes of sulfur oxidation and N-dealkylation. Excretion was determined to be 20% in the urine and 66% the in feces.

Study 028 showed that there was a longer half-life in the elderly ($t_{½}$=5.5) than in the younger adults ($t_{½}$=3.5). The differences in Cmax and AUC were less than 15 % between the elderly and younger adults; elderly men had similar values to the young adult males and females, but elderly women displayed a higher AUC (23%) and Cmax(44%). In the proposed labeling , the sponsor concluded that a dose adjustment was not necessary for age or gender.

Study 026 examined the pharmacokinetic differences in subjects with renal impairment compared to subjects with normal renal functioning. The sponsor found that ziprasidone levels were not affected by hemodialysis and that there was no statistical significance seen in the AUC and Cmax when comparing normal subjects with renally impaired subjects. The sponsor concluded that renal impairment does not alter the pharmacokinetic properties of ziprasidone; however, the biopharmaceutics review (HFD-860: 3/3/98) makes note that the sponsor used only a dosage of 20 mg bid of ziprasidone in this studies when the proposed labeling recommends 40 mg bid as the minimum dosage.

Study 030 compared pharmacokinetic properties in subjects with hepatic cirrhosis and subjects with normal hepatic functioning. There was a higher mean half-life in the subjects with cirrhosis ($t_{½}$=7.1) compared to the normal controls ($t_{½}$=4.8). Otherwise, the sponsor did not find statistical significance in the Cmax and Tmax between the groups by day 5. The sponsor's proposed labeling states that impaired liver functioning does not appreciably affect ziprasidone's pharmacokinetic properties; however, as with the renal impairment study above, the sponsor used the dose of 20 mg bid ziprasidone in this study and did not test the recommended minimum dose of 40 mg bid.

Theoretically, inducers of CYP3A4 (e.g. carbamazepine) may decrease ziprasidone exposure while inhibitors (e.g. cimetidine, ketoconazole) may increase ziprasidone levels. The sponsor's studies showed that concomitant use of carbamazepine resulted in a < 40 % decrease of ziprasidone AUC and Cmax; however, it was noted in the Biopharmaceuticals Review (3/3/98) that the sponsor used the dose of 200 mg bid (for 21 days) instead of a dose in the recommended dosage range (800 to 1200 mg qd carbamazepine); this suggests that ziprasidone levels may be even further reduced when administered concomitantly with a

therapeutic maintenance dose of 800 to 1200 mg qd carbamazepine. In vivo study 050 demonstrated that the concomitant use of ketoconazole, a potent CYP3A4 inhibitor, resulted in approximately a 30 percent increase of both AUC and Cmax of ziprasidone over placebo, suggesting that ziprasidone may have some potential to inhibit the CYP3A4 isozyme.

Concomitant use of the cimetidine and aluminum/magnesium antacids did not show clinically significant interactions with ziprasidone. Ziprasidone was shown to have no statistically significant change in the pharmacokinetics of dextromethorphan (a CYP2D6 substrate), ethinyl estradiol (a CYP3A4 substrate), and did not affect the steady state or renal clearance of lithium.

7.0 Review of Efficacy

7.1 Background

Pfizer reports they have six well controlled studies testing the effectiveness of ziprasidone in treating the psychotic symptoms of schizophrenia and schizoaffective disorders. They consider that four of these studies (106, 114, 115, and 303) are adequate to support the efficacy of ziprasidone, and that the other two studies (104 and 106) provide relevant data to their claims of effectiveness. This review will discuss the following studies which are all randomized, double blind, placebo controlled multicentered trials in subjects diagnosed with schizophrenia or schizoaffective disorder:

Study 106, n=139 total, comparing ziprasidone 20 mg bid, 60 mg bid, and placebo,
4 weeks

Study 114, n=302 total, comparing ziprasidone 40 mg bid, 80 mg bid, and placebo,
6 weeks

Study 115, n=419 total, comparing ziprasidone 20 mg bid, 60 mg bid, 100 mg bid, and placebo,
6 weeks

Study 303, n=294 total, comparing ziprasidone 20 mg bid, 40 mg bid, 80 mg bid, and placebo,
52 weeks

Study 104, n=200 total, comparing ziprasidone 5 mg bid, 20 mg bid, 40 mg bid, and placebo,
4 weeks.

Study 101 utilized the comparator control of haloperidol and will be briefly summarized, because the sponsor considered this study to be relevant to their labeling claims. There were three other controlled studies in this submission: two haloperidol controlled (studies 109 and 111) and one placebo controlled utilizing subjects with dementia (study 105); these studies were of a small size with thirty-five or less subjects.

A brief summary will be presented of the pilot study 122, an eight week, double-blind, placebo-controlled trial in the pediatric population with Tourette's Syndrome.

7.2 Review of individual studies

7.2.1 Study 106

Investigators/Location

This study was conducted in twelve centers in the United States. Please refer to Appendix 7.2.1.1 for a list of investigators and sites. The sponsor did not provide reasons why [redacted] were terminated prior to randomization of any subjects.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to evaluate the safety and efficacy of ziprasidone in treating subjects with an acute exacerbation of schizophrenia or schizoaffective disorder.

Population

Subjects chosen for this study were physically healthy males and females aged 18-64 y.o. with a DSM IIIR diagnosis of chronic or subchronic (less than one year) schizophrenia with acute exacerbation, or schizoaffective disorder (for at least a year). Females of childbearing potential were required to use effective contraception during the study. Baseline scores needed to be at least 37 on the total Brief Psychiatric Rating Scale (BPRS) and at least 4 (moderate) on 2 or more of the BPRS core items (Core items include scorings for conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.). Also required was a score of > 2 on the Clinical Global Impressions Improvement scale (CGI-I) assessed at baseline in comparison to the Clinical Global Impressions-Severity (CGI-S) score previously obtained during the screening period. The protocol allowed investigator discretion for a positive benzodiazepine or cannabinoids result in the urine drug screen; otherwise, it was required to be negative. Excluded from this study were patients with residual schizophrenia, mental retardation, organic mental syndromes, organic mental disorder, brief reactive psychosis, resistance to neuroleptic treatment (i.e. adequate trial of two or more marketed antipsychotics within two years prior to study), comorbid substance abuse/dependence within 6 months, use of depot neuroleptic within 8 weeks of beginning the study, and a high risk for suicide. Concurrent medications allowed during the double-blind trial period included lorazepam, benztropine, and beta-blockers; prohibited medications included other psychotropic drugs, antianginal agents, antiarrhythmics, antinauseants, anticoagulants (except aspirin), steroids, tryptophan, and insulin. If used chronically, antihypertensives, diuretics, hormones (except insulin), oral contraceptives, hypoglycemic agents and Zantac were allowed.

? => WD

Design

This was a randomized, double blind, placebo controlled 28 day study. After spending four to seven inpatient days in a single-blind placebo washout period, subjects were required to be inpatients for the following 21 days of the double blind placebo controlled study, and were permitted to be inpatient or outpatient for the final 7 days of the study. Psychotropic drugs other than lorazepam and a low dose beta-blocker were to be discontinued during the washout phase. A history and physical was to be performed during screening; thyroid function tests were performed at screening only. Baseline data, taken at the end of the washout period, would include vital signs (including supine and standing blood pressures), routine laboratory tests, ECG, assessment of abnormal movements (Simpson-Angus Rating Scale, Barnes Scale and AIMS), efficacy instruments (BPRS, CGI, Nurse Global Impression Scale [NGI]), and the Scale for the Assessment of Negative Symptoms (SANS).

? washout

Subjects were to be randomly assigned to one of three treatment groups: ziprasidone 20 mg bid, ziprasidone 60 mg bid, or placebo; the group taking ziprasidone 60 mg would be titrated to the target dose within five days (20 mg bid x 2 days, then 40 mg bid x 2 days followed by 60 mg bid x 24 days). Dosing was to occur with mealtime. Serum samples for pharmacokinetic analysis were to be drawn in the mornings of day 1, 7, 14, 21, and 2 hours after the morning dose on days 14 and 21. Repeat laboratory tests were to be drawn prior to dosing on the morning of days 1, 7, 14, 21,and 28. Vital signs were assessed prior to the morning dose on days 1, 2, 7, 14, 21, and 28. ECG and body weight were again recorded prior to the morning dose on days 1, 14, 28. Repeat physical exams were conducted at completion of the study.

The BPRS, CGI, and NGI were scheduled 3 to 7 hours after the morning dose on days 7, 14, 21, and 28; subjects who discontinued prior to completing were to be interviewed within 24 hours of the last dose. The SANS was also repeated on days 14 and 28 or at discontinuation.

Analysis Plan

The primary efficacy variables were defined in the protocol as the mean change in score from baseline to last visit in the following instruments: 1) the BPRS total score, 2) the BPRS core items (suspiciousness, conceptual disorganization, hallucinatory behavior, unusual thought content), and 3) the CGI- S and CGI- I scores.

The protocol states that the BPRS total score was to be analyzed with an analysis of variance with treatment, center, and their interaction. CGI was to be analyzed nonparametrically as a discrete variable.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 203 subjects screened to enter the study, 139 subjects were randomized to one of the three treatment groups and had at least one dosage of double blind treatment. Reasons for not being chosen to participate in this trial were not provided in this submission.

The following table from the sponsor's study report itemizes reasons for discontinuations in the three treatment groups:

Discontinuations from Study
Ziprasidone Protocol 106

	Ziprasidone 20 mg BID	Ziprasidone 60 mg BID	Placebo
Number of Subjects Randomized	44	47	48
Number of Subjects Discontinued			
Related to Study Drug	11	10	12
Insufficient clinical response	11	8	12
Adverse event	0	1	0
Laboratory test abnormality	0	1	0
Not related to Study Drug	5	13	12
Adverse event	1	3	0
Protocol violation	2	2	2
Lost to follow-up	0	1	0
Withdrawn consent	1	5	9
Other	1	2	1
TOTAL	16	23	24

Appendix 7.2.1.2 shows the number of subjects per week who completed each treatment group; the reviewing statistician, Dr. Sue-Jane Wang, explained that the sample size under the "Treated" column and the "Week 1" column differ because there were subjects who did not complete the first seven days of the study. The sponsor defines their intent-to-treat as any subject who had baseline measurements and at least one post-baseline measurement; according to Dr. Wang, the sample size used in the efficacy analysis varied depending on the data available for each efficacy endpoint.

The rate of dropout for the treatment group taking ziprasidone 60 mg bid is almost identical to the profile of dropouts for placebo showing approximately a fifty percent withdraw by the end of the study. However, the group taking ziprasidone 20 mg bid appeared to have slightly fewer dropouts, with a sixty-four percent completer rate.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males with mean ages of approximately 40 years old. The mean ages of the female subjects were higher than the male subjects for all treatment groups. There did not appear to be imbalances in the treatment groups. Appendix 7.2.1.3 shows the breakdown of demographics by treatment group.

The mean baseline values for the BPRS Total Score, BPRS Core Items, CGI -S, and CGI-I were very close, if not identical when comparing placebo with the two treatment groups (please refer to table below). The sponsor did not provide any statistical comparisons of baseline values.

Mean Baseline Values of Primary Efficacy Variables

MEAN SCORE	ZIPRASIDONE		PLACEBO
	20 MG BID	60 MG BID	
BPRS Total	36.5	36.6	37
BPRS Core	13.4	13.6	13.9
CGI-S	4.7	4.7	4.7

Concomitant Medications

Lorazepam was taken by the majority of subjects in all treatment groups. Please refer to the table below for select concomitant medication use.

Selected concomitant medication used in Study 106

	Ziprasidone		
	20 mg bid (n=44)	60 mg bid (n=47)	Placebo (n=48)
Lorazepam	36	40	43
Benztropine	3	9	4
Beta-Blocker	3	3	2
Antidepressant	0	1	0
Antipsychotic	2	1	2
Antihistamine	1	6	3

During the double-blind trial, lorazepam was used with a mean total cumulative dosage of 53 mg for the 36 subjects in the 20 mg bid group; 43 mg of lorazepam was the mean usage in the 60 mg bid group, while the placebo group had a mean usage of 30 mg. Benztropine was taken by 3 subjects in the 20 mg bid group with a mean dose of 15 mg during the trial; 14 mg was the mean dose for the 60 mg bid group, and the placebo group used a mean dosage of 5.5 mg.

Efficacy Results

Please refer to Appendix Tables for results of the important outcome measures (BPRS Total, BPRS Core, CGI-S, and SANS). The ziprasidone 60 mg bid group was the only group that showed statistical significance in week 4 for the primary efficacy variables of the BPRS Total and the CGI-S for both OC and LOCF when compared with placebo. However, neither of the treatment groups provided statistical

significance with the BPRS Core or the SANS with a 95% confidence interval when compared with placebo.

Miscellaneous Issues

Serum plasma levels of ziprasidone were obtained during this study. On day 21, the mean trough level for the ziprasidone 20 mg bid group was 18.6 ng/ml, and for the ziprasidone 60 mg bid group, the mean level was 56.4 ng/ml.

The sponsor performed an interim analysis which they state did not modify the design of the study.

Conclusions

Because this study showed statistical significance in only two of the three primary efficacy variable in week four only, it merely provides fair evidence for the antipsychotic properties of ziprasidone at a dose of 60 mg bid.

7.2.2 Study 114

Investigators/Location

This study was conducted in thirty-four centers in the United States and Canada. Please refer to **Appendix Table 7.2.2.1** for a list of investigators and sites.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to evaluate the safety and efficacy of ziprasidone in treating subjects with an acute exacerbation of schizophrenia or schizoaffective disorder.

Population

Entrance criteria were similar to Study 106 with the exception that this study required a baseline score of > 59 for the total score of the Positive and Negative Syndrome Scale (PANSS). Please refer to Study 106 for a list of concurrent medications permitted during the double-blind trial period.

Design

This was a randomized six week, double blind, placebo controlled study. Subjects who met entry criteria were required to undergo an inpatient single-blind placebo washout period for 3-7 days followed by 14 days of inpatient double-blind treatment. During the remaining 28 days of the study, subjects could be inpatient or outpatient during which time they would be evaluated at weekly visits. A history and physical was to be performed during screening; thyroid function tests were performed at screening only. Baseline data, taken at the end of the washout period, would include vital signs (including sitting and standing), routine laboratory tests, ECG, assessment of abnormal movements (Simpson-Angus Rating Scale, Barnes Scale and AIMS), and efficacy instruments (PANSS, CGI, and the Montgomery-Asberg Depression Rating Scale [MADRS]).

Once chosen for the study, subjects were to be randomized to one of three treatment groups: 1) ziprasidone 40 mg bid, 2) ziprasidone 80 mg bid 3) placebo. The double-blind medication was to be administered orally two times a day (dosing spaced about 12 hours apart) with food. Titration occurred over a period of

3 days for the 80 mg bid group (40 mg x 2 days, then 80 mg x 40 days). Serum samples for pharmacokinetic analysis were to be drawn pre-dosing of days 7,14, 42, or at early termination. Repeat laboratory tests were to be drawn on days 7, 21, 42, or at early termination. Vital signs were assessed on days 7, 14, 21, 28, 35 and 42. ECG were again recorded on days 14 and 42 or at early termination. Repeat physical exams were conducted at completion of the study.

The PANSS and the CGI-S were to be given weekly, and the MADRS would be repeated on days 7, 14, 21, and 42. Subjects who discontinued prior to completing were to be interviewed within 24 hours of the last dose.

Analysis Plan

The primary efficacy variables specified in the protocol were the total score of the BPRS derived from the PANSS (BPRSd), BPRSd core items (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content) and the CGI-S. Secondary efficacy variables included the PANSS-total, PANSS negative sub-scale, the CGI-I, and the MADRS.

The protocol stated that linear models will be fitted to the primary efficacy variables analyzing baseline values and treatment centers. The protocol also states that an analysis of discrete or categorical data may be used as an alternative method.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 440 subjects screened to enter the study, 302 subjects were randomized to one of the three treatment groups and had at least one dosage of double blind treatment. Reasons for not being chosen to participate in this trial were not provided in this submission.

The following table from the sponsor's study report itemizes reasons for discontinuations in the three treatment groups:

Discontinuations from Study
Ziprasidone Protocol 114

	Ziprasidone 40 mg BID		Ziprasidone 80 mg BID		Placebo	
Number of Subjects Randomized	106		104		92	
Number of Subjects (%) Discontinued						
Related to Study Drug	27	(25.5)	23	(22.1)	32	(34.8)
Insufficient clinical response	26	(24.5)	16	(15.4)	32	(34.8)
Adverse event	1	(0.9)	7	(6.7)	0	(0.0)
Not Related to Study Drug	25	(23.6)	14	(13.5)	15	(16.3)
Adverse event	1	(0.9)	1	(1.0)	1	(1.1)
Protocol violation	3	(2.8)	1	(1.0)	1	(1.1)
Lost to follow-up	6	(5.7)	2	(1.9)	3	(3.3)
Does not meet randomization criteria	0	(0.0)	3	(2.9)	1	(1.1)
Withdrawn consent	15	(14.2)	6	(5.8)	8	(8.7)
Other	0	(0.0)	1	(1.0)	1	(1.1)
TOTAL	52	(49.1)	37	(35.6)	47	(51.1)

Appendix 7.2.2.2 shows the number of subjects per week who completed each treatment group; the reviewing statistician, Dr. Sue-Jane Wang, explained that the sample size under the "Treated" column and the "Week 1" column differ because there were subjects who did not complete the first seven days of the study. The sponsor defines their intent-to-treat as any subject who had baseline measurements and at least one post-baseline measurement; according to Dr. Wang, the sample size used in the efficacy analysis varied depending on the data available for each efficacy endpoint.

The dropout rate was lowest for the treatment group taking ziprasidone 80 mg bid with a sixty-four percent completer rate. The withdrawal rate for both the placebo and ziprasidone 40 mg bid treatment group was approximately fifty percent by the end of the study.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males with mean ages of approximately 36 years old in all groups. The mean ages of the female subjects were higher than the male subjects for all treatment groups. There did not appear to be imbalances in the treatment groups. Appendix 7.2.2.3 shows the breakdown of demographics by treatment group.

The mean baseline values for the BPRSd Total Score, BPRSd Core Items, CGI -S, and PANSS were comparable (please refer to table below). The sponsor did not provide any statistical comparisons of baseline values.

Mean Baseline Values of Primary Efficacy Variables

MEAN SCORE	ZIPRASIDONE		PLACEBO
	40 MG BID	80 MG BID	
BPRSd Total	56.5	55.0	55.1
BPRSd Core	16.9	16.6	16.4
CGI-S	4.8	4.8	4.8
PANSS total	98.2	95.8	97.3
PANSS neg.	25.4	24.3	24.9

Concomitant Medications

Lorazepam was taken by the majority of subjects in all treatment groups. Please refer to the table below for select concomitant medication use.

Selected concomitant medication used in Study 114

	Ziprasidone		
	40 mg bid (n=106)	80 mg bid (n=104)	Placebo (n=92)
Lorazepam	90	96	85
Benztropine	21	26	12
Beta-Blocker	5	10	3
Antihistamine	3	3	1
Rx for alcoholism and drug addiction	2	8	1

The sponsor did not provide dosages of lorazepam and benztropine use for this study.

Efficacy Results

Please refer to Appendix Tables for results of the important outcome measures (BPRSd Total, BPRSd core items, CGI-Severity, and PANSS). When compared with placebo at a 95% confidence interval, both ziprasidone treatment groups showed statistical significance by week six for efficacy variables of the BPRSd Total, BPRSd core items, CGI-S, and PANSS total for LOCF. For OC, the only statistically significant result at week six was the CGI-S for the ziprasidone 80 mg bid group.

Miscellaneous Issues

This study included data that was generated from a study site ( ) with the investigators Drs. . . The sponsor recalculated the efficacy data of Study 114 excluding data submitted from study site they concluded that the efficacy data was not significantly affected by the exclusion of Dr. . data.

This efficacy review of study 114 includes data from site . The only noteworthy observation from the analysis of the data without study site is that there was no statistically significant findings at week 6 for the ziprasidone 40 mg bid treatment group.

Serum plasma levels of ziprasidone were obtained during this study. On day 42, the mean trough level for the ziprasidone 40 mg bid group was 47 ng/ml, and for the ziprasidone 80 mg bid group, the mean level was 109 ng/ml.

Conclusions

This study demonstrated statistical significance when comparing both the treatment groups and placebo in the three primary efficacy variables by week six. These results provide evidence that ziprasidone is effective in treating the acute symptoms of psychosis associated with schizophrenia or schizoaffective disorder. Results for the 80 mg bid group were generally superior to the 40 mg bid group results.

7.2.3 Study 115

Investigator(s)/Location

This study was conducted in 54 sites in the United States. Please refer to the sponsor's list of investigators and sites in Appendix 7.2.3.1. The sponsor did not provide reasons for terminating prior to randomization of any subjects.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to assess the safety and efficacy of ziprasidone in treating subjects with an acute exacerbation of schizophrenia or schizoaffective disorder as compared to placebo and haloperidol.

Population

Please refer to Study 114 which had the same entrance criteria. Concurrent medications were similar to those used in previous studies.

Design

This was a randomized, double-blind, placebo controlled, six week study. The details of this study's design were similar to Study 114 (please refer to Study 114 for more information).

Once chosen for the study, subjects were to be randomized to one of five treatment groups: 1) ziprasidone 20 mg bid, 2) ziprasidone 60 mg bid 3) ziprasidone 100 mg bid, 4) haloperidol 15 mg qd, and 5) placebo. The double-blind medication was to be administered orally two times a day (dosing spaced about 12 hours apart) with food. Titration occurred over a period of 3 days for the 60 mg bid group (40 mg x 2 days, then 60 mg x 40 days) and over a period of 5 days for the 100 mg bid group (40 mg bid x 2 days, then 80 mg

bid x 2 days, followed by 100 mg bid x 38 days). Serum samples for pharmacokinetic analysis were to be drawn pre-dosing on days 7,14, 42, or at early termination, and, also, at specified time intervals after dosing (i.e. 1-4 , 4-7, or 7-10 hours) on days 14 and 21. Repeat laboratory tests were to be drawn on days 7,14, 42, or at early termination. Vital signs were assessed on days 7, 14, 21, 28, 35 and 42. ECGs were repeated on days 14 and 42 or at early termination. Another physical exam was to be conducted at completion of the study.

The PANSS, CGI-S, and CGI-I were to be given weekly; the MADRS would be repeated on days 7, 14, 21, and 42. Subjects who discontinued prior to completing were to be interviewed within 24 hours of the last dose.

Analysis Plan

The primary efficacy variables were the BPRSd total score (derived from the PANSS), BPRSd core items and the CGI-S. Secondary efficacy variables included the PANSS-total, PANSS negative sub-scale, the CGI-I, and discontinuation status due to lack of efficacy.

The protocol stated that a linear model investigating the dose-response relationship across the ziprasidone and placebo treatment groups would be used. This analysis would use the baseline values of the primary efficacy variables as a covariate and also look at interaction effects between centers and treatment. It is also noted that there were several amendments made to the analysis section of the protocol.

Study Conduct/Outcome

Patient Disposition

Of the 567 subjects screened to enter the study, 419 were randomized to one of the three treatment groups and had at least one dosage of double blind treatment. Reasons for not being chosen to participate in this trial were not provided in this submission.

The following table from the sponsor's study report itemizes reasons for discontinuations in the five treatment groups:

Discontinuations from Study
Ziprasidone Protocol 115

	Ziprasidone 20 mg BID		Ziprasidone 60 mg BID		Ziprasidone 100 mg BID	
Number of Subjects Randomized	87		78		86	
Number of Subjects (%) Discontinued						
Related to Study Drug	22	(25.3)	26	(33.3)	22	(25.6)
Insufficient clinical response	22	(25.3)	22	(28.2)	18	(20.9)
Adverse event	0	(0.0)	2	(2.6)	4	(4.7)
Laboratory test abnormality	0	(0.0)	2	(2.6)	0	(0.0)
Not Related to Study Drug	15	(17.2)	13	(16.7)	16	(18.6)
Adverse event	1	(1.1)	1	(1.3)	2	(2.3)
Protocol violation	0	(0.0)	2	(2.6)	0	(0.0)
Lost to follow-up	3	(3.4)	0	(0.0)	1	(1.2)
Does not meet randomization criteria	1	(1.1)	1	(1.3)	2	(2.3)
Withdrawn consent	10	(11.5)	8	(10.3)	10	(11.6)
Other	0	(0.0)	1	(1.3)	1	(1.2)
TOTAL	37	(42.5)	39	(50.0)	38	(44.2)

Discontinuations from Study
Ziprasidone Protocol 115

	Haloperidol		Placebo	
Number of Subjects Randomized	85		83	
Number of Subjects (%) Discontinued				
Related to Study Drug	19	(22.4)	35	(42.2)
Insufficient clinical response	13	(15.3)	35	(42.2)
Adverse event	6	(7.1)	0	(0.0)
Laboratory test abnormality	0	(0.0)	0	(0.0)
Not Related to Study Drug	18	(21.2)	21	(25.3)
Adverse event	1	(1.2)	3	(3.6)
Protocol violation	0	(0.0)	2	(2.4)
Lost to follow-up	2	(2.4)	1	(1.2)
Does not meet randomization criteria	1	(1.2)	1	(1.2)
Withdrawn consent	13	(15.3)	14	(16.9)
Other	1	(1.2)	0	(0.0)
TOTAL	37	(43.5)	56	(67.5)

Appendix 7.2.3.2 shows the number of subjects per week who completed each treatment group; the reviewing statistician, Dr. Sue-Jane Wang, explained that the sample size under the "Treated" column and the "Week 1" column differ because there were subjects who did not complete the first seven days of the study. The sponsor defines their intent-to-treat as any subject who had baseline measurements and at least one post-baseline measurement; according to Dr. Wang, the sample size used in the efficacy analysis varies depending on the data available for each efficacy endpoint.

The completer rate was highest for the ziprasidone 60 mg bid group (64%), and, as expected, lowest in the placebo group (32%). The other three groups had approximately a 45% withdraw by the end of the study.

Demographics/Group Comparability

The majority of patients in this study were Caucasian males with mean age of approximately 40 years old. There did not appear to be any imbalances in the treatment groups. Appendix 7.2.3.3 shows the breakdown of demographics by treatment group.

The mean baseline values for the BPRSd total score, BPRSd core items, CGI -S, and PANSS were comparable (please refer to table below). The sponsor did not provide any statistical comparisons of baseline values.

Mean Baseline Values of Primary Efficacy Variables

MEAN SCORE	ZIPRASIDONE			PBO	HALDOPERIDAL
	20 MG BID	60 MG BID	100 MG BID		15 MG
BPRSd Total	53.8	51.8	51.8	54.3	53.9
BPRSd Core	16.1	16.0	15.9	16.6	16.2
CGI-S	4.9	4.9	4.7	4.9	5.0
PANSS total	93.2	90.4	89.5	93.3	94.1
PANSS neg.	22.9	23.4	22.5	22.4	24.1

Concomitant Medications

Lorazepam was taken by the majority of subjects in all treatment groups. Please refer to the table below for select concomitant medication use.

Selected concomitant medication used in Study 115

	Ziprasidone			Haloperidol	
	20 mg bid (n=87)	60 mg bid (n=78)	100 mg bid (n=86)	15 mg (n=85)	Placebo (n=83)
Lorazepam	76	69	75	76	75
Benztropine	24	15	36	43	26
Beta-Blocker	7	7	7	16	6
Antidepressant	0	0	0	0	0
Antipsychotic	2	4	1	5	9
Antihistamine	0	2	0	1	0

The sponsor did not provide dosages of lorazepam and benztropine use for this study.

Efficacy Results

Please refer to Appendix Tables for results of the important outcome measures (BPRSd Total, BPRSd Core, CGI-S, and PANSS). All treatment groups showed statistical significance by week 6 for efficacy variables of the BPRSd Total, BPRSd core items, CGI-S, and PANSS Negative total for LOCF, but not for OC when compared to placebo at a 5% significance level. In week six, the PANSS negative showed statistical significance for LOCF in the ziprasidone 100 mg bid and haloperidol groups only.

Miscellaneous Issues

Serum plasma levels of ziprasidone were obtained during this study. For the ziprasidone 20 mg bid treatment group, the mean trough serum concentrations were 28 ng/ml; the mean trough levels for the ziprasidone 60 mg bid group was 62 ng/ml, and the ziprasidone 100 mg bid treatment group had a mean trough level of 111 ng/ml.

The following table from the sponsor's submission lists the pharmacokinetic parameters established as a result of 825 samples from 237 subjects:

Pharmacokinetic Parameter		Estimated Value	Standard error	% CV
Systemic clearance	CL/F (L/hr)	53.5	1.25	2.34
Volume of central compartment	V_c/F (L)	381	65.2	17.1
Absorption coefficient	K_a (1/hr)	0.661	0.147	22.2
Volume of peripheral compartment	V_p/F (L)	1430	951	66.5
Intercompartmental clearance	Q (1/hr)	76.5	10.8	14.1
Absorption lag time	LAG (hr)	1.41	0.012	0.850

The sponsor claims that a dose response relationship among the three ziprasidone treatment groups and placebo were found to be statistically significant for all primary efficacy variables. This dose response was found when the ziprasidone treatment groups were compared to placebo. However, when comparing the ziprasidone treatment groups with each other, it does not appear that increasing doses yielded higher scores on efficacy variables.

Also of note is that the number of centers was increased to 54 where as the protocol estimated 30-40 centers.

Conclusions

This study demonstrated statistical significance when comparing all the treatment groups with placebo in the three primary efficacy variables at week six. These results provide evidence that ziprasidone is effective in treating the acute symptoms of psychosis associated with schizophrenia or schizoaffective

disorder. Results were generally similar between ziprasidone dose groups. The haloperidol arm results (including negative symptoms) were numerically superior to the ziprasidone groups.

This pharmacokinetic data supports the sponsor's claim that ziprasidone follows linear kinetics.

7.2.4 Study 303

Investigator(s)/Location

Appendix 7.2.4.1 gives the sponsor's list of 33 sites designated for this study; however, the study was conducted in 29 of these centers in Europe (Czech Republic, Estonia, Hungary and Poland). The sponsor did not provide reasons for closing the) prior to subject randomization.

Study Plan

Objective(s)/Rationale

The objectives of this fifty-two week study were to assess relapse prevention of psychotic episodes in hospitalized subjects with schizophrenia and to assess the safety and efficacy of ziprasidone compared to placebo.

Population

Subjects chosen for this study included physically healthy males and females aged 18 years or older who had been hospitalized at least two months prior to entry into the study with a primary diagnosis of chronic or subchronic schizophrenia. Females of childbearing potential were required to use methods of birth control that include an IUD, implanted or oral contraceptive methods. A baseline score of five or less on the CGI-S was required for inclusion in this trial. The protocol allowed investigator discretion for positive benzodiazepine or cannabinoids result in the urine drug screen; otherwise, it was required to be negative. Excluded from this study were patients scoring ≥ five (moderate severe) on the hostility or uncooperativeness items of the PANSS, with a history of psychosurgery, mental retardation, organic mental syndromes, organic mental disorder, brief reactive psychosis, epilepsy, resistance to neuroleptic treatment (i.e. adequate trial of two or more marketed antipsychotics within two years prior to study), comorbid substance abuse/dependence within 3 months, and a high risk for suicide or homicide. Concurrent medications allowed during the double-blind trial period included lorazepam, temazepam, anticholinergic medication, and beta-blockers. Other psychotropic drugs were prohibited.

Design

This study was a randomized, double blind, placebo controlled, fifty-two week inpatient study. Subjects who met entry criteria were required to undergo an inpatient single-blind placebo lead-in for 3 days followed by 52 weeks of inpatient double-blind treatment. Screening included a history and physical (including sitting and standing vital signs), routine laboratory tests, ECG, and an ophthalmology assessment (including a funduscopy and a slit-lamp examination). Baseline data, taken at the end of the lead-in period included assessment of abnormal movements (Simpson-Angus Rating Scale, Barnes Scale and AIMS) and efficacy instruments (PANSS, CGI, and Global Assessment of Functioning [GAF])

Once chosen for the study, subjects were to be randomized to one of four treatment groups: 1) ziprasidone 20 mg bid, 2) ziprasidone 40 mg bid 3) ziprasidone 80 mg bid, and 4) placebo. The double-blind medication was to be administered orally twice daily postprandially. Titration occurred over a period of 3 days for the 80 mg bid group (40 mg x 2 days, then 80 mg for the remainder of the study). Serum samples for pharmacokinetic analysis and repeat laboratory tests were to be drawn at weeks 4, 12, 28, and 52 or at early termination; thyroid function tests were done at screening and at week 52 only. Vital signs were

assessed at weeks 2, 4,12, 28, 40, and 52. ECGs were again recorded at weeks 12, 28, 52 or at early termination. Repeat physical exams and ophthalmology assessments were repeated at completion of the study.

The PANSS, CGI, and assessments for abnormal movements were administered at weeks 3, 6, 16, 28, 40, and 52; the GAF was evaluated at weeks 28 and 52.

Analysis Plan

The protocol states that the primary efficacy variable is the measurement of time to impending psychotic relapse. The sponsor defines "impending relapse" as CGI-I score of 6 (much worse) or greater and/or a score of 6 (severe) or greater on either of the PANSS items P7 (hostility) or G8 (uncooperativeness) on two successive days. A score of 5 (minimally worse) on the CGI-I would require ratings to be done on the following three days. If the CGI score remained at 5, then CGI ratings would be performed at weekly intervals until the score improved to 4 or less and then ratings could be performed according to the study schedule.

Other efficacy variables included the PANSS, CGI, and GAF.

The Kaplan-Meier analysis and the Cox proportional hazards model were to be used to analyze the time to discontinuation. ANCOVA models were to be used for continuous and most of the categorical efficacy variables. The analysis plans would look at the interaction effects of treatment groups.
Study Conduct/Outcome

Patient Disposition

Of the 351 subjects screened to enter the study, 294 were randomized to one of the four treatment groups and had at least one dosage of double blind treatment. Reasons for not being chosen to participate in this trial were not provided in this submission.

The following tables from the sponsor's study report itemizes reasons for discontinuations in the four treatment groups:

Discontinuations from Study
Ziprasidone Protocol 303

	Ziprasidone 20 mg BID		Ziprasidone 40 mg BID		Ziprasidone 80 mg BID		Placebo	
Number of Subjects Randomized	76		72		71		75	
Number of Subjects (%) Discontinued								
Related to Study Drug	33	(43.4)	28	(38.9)	27	(38.0)	50	(66.7)
Insufficient clinical response	27	(35.5)	22	(30.6)	24	(33.8)	43	(57.3)
Adverse event	6	(7.9)	6	(8.3)	1	(1.4)	6	(8.0)
Laboratory test abnormality	0	(0.0)	0	(0.0)	2	(2.8)	1	(1.3)
Not Related to Study Drug	9	(11.8)	13	(18.1)	11	(15.5)	11	(14.7)
Adverse event	1	(1.3)	1	(1.4)	4	(5.6)	5	(6.7)
Laboratory test abnormality	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Lost to follow-up	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Withdrawn consent	4	(5.3)	5	(6.9)	5	(7.0)	1	(1.3)
Special safety test	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Other	4	(5.3)	5	(6.9)	2	(2.8)	4	(5.3)
TOTAL	42	(55.3)	41	(56.9)	38	(53.5)	61	(81.3)

Appendix 7.2.4.2 shows the number of subjects who completed each treatment group at specified intervals; the reviewing statistician, Dr. Sue-Jane Wang, explained that the sample size under the "Treated" column and the "Week 1" column differ because there were subjects who did not complete the first seven days of the study. The sponsor defines their intent-to-treat as any subject who had baseline measurements and at least one post-baseline measurement; according to Dr. Wang, the sample size used in the efficacy analysis varies depending on the data available for each efficacy endpoint.

The three ziprasidone groups had similar discontinuation rates with 46% of subjects completing both the 20 mg bid and 40 mg bid group, and 48% of subjects completing the 60 mg bid group. As expected, the completer rate was lowest for the placebo group (19%).

Demographics/Group Comparability

All patients were Caucasian; the mean ages was approximately 37 years old. The mean ages of the female subjects were higher than the male subjects for all treatment groups. There did not appear to be imbalances in the treatment groups. Appendix 7.2.4.3 shows the breakdown of demographics by treatment group.

The mean baseline values for the BPRSd total score, BPRSd core items, CGI -S, and PANSS were comparable (please refer to table below). The sponsor did not provide any statistical comparisons of baseline values.

Mean Baseline Values of Primary Efficacy Variables

MEAN SCORE	ZIPRASIDONE			PLACEBO
	20 MG BID	40 MG BID	80 MG BID	
BPRSd Total	46.1	47.1	45.9	48.0
BPRSd Core	11.2	11.7	11.2	11.7
CGI-S	4.0	4.0	4.0	4.1
PANSS total	85.1	86.6	85.2	88.9
PANSS neg.	24.9	24.7	25.0	25.7

Concomitant Medications

Lorazepam was taken by the majority of subjects in all treatment groups. Please refer to the table below for select concomitant medication use.

Selected concomitant medication used in Study 303

	Ziprasidone			
	20 mg bid (n=76)	40 mg bid (n=72)	80 mg bid (n=71)	Placebo (n=75)
Lorazepam	46	39	41	50
Antimuscarinic Drug for Parkinsonism	12	9	14	10
Beta-Blocker	4	1	2	1
Antidepressant	0	1	0	0
Antipsychotic	0	1	0	1
Antihistamine	0	0	0	1

The sponsor did not provide dosages of lorazepam and benztropine use for this study.

Efficacy Results

The rate of relapse (as defined in the analysis section above) was lower in the ziprasidone groups (mean of 33%) than in the placebo group (57%). Compared to placebo, the three group showed a statistically significant less risk of relapse in the ziprasidone groups; however, there was no significant difference in the risk when comparing the three different ziprasidone dosage groups. (please refer to Appendix Table for details).

Please refer to Appendix Tables for results of the other important outcome measures (BPRSd total, BPRSd core, CGI-S, PANSS total and PANSS neg.). By week 52, all ziprasidone treatment groups showed

statistically significant improvement in these score for LOCF, but not for OC when compared to placebo at a 5% significance level.

Miscellaneous Issues

Serum plasma levels of ziprasidone were obtained during this study. For the ziprasidone 20 mg bid treatment group, the mean trough serum concentrations were 26 ng/ml; the mean trough levels for the ziprasidone 40 mg bid group was 49 ng/ml, and the ziprasidone 80 mg bid treatment group had a mean trough level of 82 ng/ml.

Conclusions

It is debatable if the sponsor has proven that ziprasidone is superior to placebo in the prevention of relapse. Their definition of "relapse" and this study design do not follow traditional methods of proving relapse prevention. There is no presumption that subjects were stable at the beginning of the study nor were subjects selected as responders in an open label study. However, the fact that subjects were hospitalized for two months prior to the start of the study may suggest that subjects had been somewhat stable prior to initiation of the study, and Dr. Wang (HFD 710:11/24/97) concluded that, using the definitions of the sponsor, the ziprasidone treatment group showed a longer time to relapse than placebo that was statistically significant.

Trade & descr

The results from the other efficacy variables in this study provide support to the efficacy of ziprasidone in the treatment of psychosis in schizophrenia.

7.2.5 Study 104

Investigators/Location

This study was conducted in seventeen centers in the United States. Please refer to Appendix 7.2.5.1 for a list of investigators and sites. closed prior to randomization of subjects.

Study Plan

Objective(s)/Rationale

The primary objective of this twenty-eight day, double blind, placebo controlled study was to evaluate the safety and efficacy of ziprasidone in treating subjects with an acute exacerbation of schizophrenia or schizoaffective disorder.

Population

Subjects chosen for this study were physically healthy males and females aged 18-64 y.o. Please refer to Study 106 for details of the entrance criteria and a list of concurrent medications allowed during the double-blind trial period.

Design

This is a randomized double-blind placebo controlled 28 day study. For details of the general study design and concomitant medications, please refer to Study 106.

After the lead-in phase, subjects were to be randomly assigned to one of four treatment groups: ziprasidone (CP-88,059-1) ziprasidone 5 mg bid, 2) ziprasidone 20 mg bid, 3) ziprasidone 40 mg bid, or 4) placebo;

the group taking ziprasidone 40 mg would be titrated to the target dose within four days (20 mg bid x 3 days, then 40 mg bid for the remainder of the study).

Analysis Plan

The primary efficacy variables were defined as the mean change in score from baseline to last visit in the following instruments: 1) the BPRS total score, 2) psychotic core items, and 3) the CGI- S.

The protocol states that the BPRS total score was to be analyzed with an analysis of variance with treatment, center, and their interaction. CGI was to be analyzed nonparametrically, as a discrete variable.

Other efficacy variables included the Nurses Global Impression (NGI).

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 303 subjects screened to enter the study, 200 subjects were randomized to one of the four treatment groups and had at least one dosage of double blind treatment. Reasons for not being chosen to participate in this trial were not provided in this submission.

The following table from the sponsor's study report itemizes reasons for discontinuations in the three treatment groups:

Discontinuations from Study
Ziprasidone Protocol 104

	Ziprasidone 5mg BID	Ziprasidone 20mg BID	Ziprasidone 40mg BID	Placebo
Number of Subjects Randomized	47	55	48	50
Number of Subjects (%) Discontinued				
Related to Study Drug	11 (23.4)	16 (29.1)	17 (35.4)	17 (34.0)
Insufficient clinical response	11 (23.4)	16 (29.1)	15 (31.3)	16 (32.0)
Adverse event	0 (0.0)	0 (0.0)	2 (4.2)	1 (2.0)
Not related to Study Drug	6 (12.8)	13 (23.6)	11 (22.9)	6 (12.0)
Adverse event	2 (4.3)	0 (0.0)	0 (0.0)	1 (2.0)
Laboratory test abnormality	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Protocol violation	3 (6.4)	5 (9.1)	5 (10.4)	0 (0.0)
Withdrawn consent	0 (0.0)	7 (12.7)	5 (10.4)	4 (8.0)
Other	1 (2.1)	0 (0.0)	1 (2.1)	1 (2.0)
TOTAL	17 (36.2)	29 (52.7)	28 (58.3)	23 (46.0)

Appendix 7.2.5.2 shows the number of subjects per week who completed each treatment group; the reviewing statistician, Dr. Sue-Jane Wang, explained that the sample size under the "Treated" column and the "Week 1" column differ because there were subjects who did not complete the first seven days of the study. The sponsor defines their intent-to-treat as any subject who had baseline measurements and at least one post-baseline measurement; according to Dr. Wang, the sample size used in the efficacy analysis varies depending on the data available for each efficacy endpoint.

The dropout rate was lowest for the treatment group taking ziprasidone 5 mg bid (36%). The remaining treatment groups demonstrated a dropout rate of approximately fifty percent by the end of the study.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males with mean ages of approximately 40 years old. The mean ages of the female subjects were higher than the male subjects for all treatment groups. There did not appear to be imbalances in the treatment groups. Appendix 7.2.5.3 shows the breakdown of demographics by treatment group.

The mean baseline values for the BPRS total score, BPRS core items, CGI -S, and CGI-I had similar scores across all treatment groups (please refer to table below). The sponsor did not provide any statistical comparisons of baseline values.

Mean Baseline Values of Primary Efficacy Variables

MEAN SCORE	ZIPRASIDONE			PLACEBO
	5 MG BID	20 MG BID	40 MG BID	
BPRS Total	34.1	34.5	36.2	33.4
BPRS Core	12.8	13.0	12.8	13.7
CGI-S	4.9	4.8	4.9	5.0

Concomitant Medications

Lorazepam was taken by the majority of subjects in all treatment groups. Please refer to the table below for select concomitant medication use.

Selected concomitant medication used in Study 104

	Ziprasidone			
	5 mg bid (n=47)	20 mg bid (n=55)	40 mg bid (n=48)	Placebo (n=50)
Lorazepam	34	42	39	41
Benztropine	6	11	6	8
Beta-Blocker	4	2	1	3
Antidepressant	0	1	0	0
Antipsychotic	5	3	3	4
Antihistamine	1	1	0	3

During the double-blind trial, lorazepam was used with an mean cumulative dosage of 60 mg for the 34 subjects in the 5 mg bid group; 40.5 mg of lorazepam was the mean usage in the 20 mg bid group, while the 40 mg bid group had a mean dosage of 46 mg of lorazepam. The placebo group had a mean dose of 43 mg of lorazepam. Benztropine was taken by the 6 subjects in the 5 mg bid group with a mean dose of 20.5 mg during the trial; 15 mg was the mean dose for the 20 mg bid group, and the 40 mg bid group took a mean dose of 41.5 mg. The placebo group used a mean dosage of 24 mg of benztropine.

Efficacy Results

Please refer to Appendix Tables for results of the important outcome measures (BPRS total, BPRS core, CGI-S). Statistical significance when compared with placebo was seen only in the ziprasidone 20 mg bid treatment group in the BPRS total and core for OC. Otherwise, no other parameters proved to be statistically significant in this trial.

Miscellaneous Issues

Serum plasma levels of ziprasidone were obtained during this study. At week four, the mean concentration of ziprasidone found in the 5 mg bid group was 3.7 ng/ml; the 20 mg bid group had a mean ziprasidone concentration of 29.7 ng/ml , while the ziprasidone 40 mg bid group had a mean plasma concentration of 34.8 ng/ml.

Conclusions

This study did not provide evidence for the efficacy of ziprasidone in the treatment of an acute exacerbation of schizophrenia or schizoaffective disorder. One possible reason for these negative results is that the baseline scores in this study were lower (i.e. subjects may have been less ill) than baseline scores in studies with more positive results.

7.2.6 Other Studies

Study 101 was a four week, double-blind, haloperidol controlled trial conducted in six US centers. Ninety subjects diagnosed with schizophrenia and schizoaffective disorder were randomized to one of 5 groups: 1) ziprasidone 2 mg bid, 2) 5 mg bid, 3) 20 mg bid, 4) 80 mg bid, or 5) haloperidol 15 mg. Efficacy variables included were the BPRS, CGI, NGI, and Nurses Observation Scale for Inpatient Evaluation (NOSIE). In the protocol, a primary efficacy variable was only identified as the changes from baseline to last observation. Results from this study do not support the efficacy of ziprasidone, because no differences were found when comparing each treatment with the lowest dosage group.

7.2.7 Pediatric Studies

Study 122 was a double blind, placebo controlled, 8 week flexible dose (maximum: 20 mg bid ziprasidone) pilot study in 16 pediatric subject (ages 7-16) with Tourette's Syndrome to test the effectiveness of ziprasidone in treating their symptoms of Tourette's Syndrome. Results showed that there was statistical significance seen in one primary efficacy variable (Yale Global Tic Severity Scale), but statistical significance was not demonstrated in the other primary efficacy variable (Clinical Global Impression Severity Scale for TS) when comparing improvement of subjects in the ziprasidone treatment group with placebo .

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

When exploring how demographic characteristics may have affected the efficacy data, the sponsor claims to have found no significant effect on treatment based on age, gender, or race. The p-values are not significant for the interaction effects of age (<55 years or ≥ 55 years), gender, race (Caucasian or African American) and any of the efficacy variables tested (PANSS total, PANSS negative, BPRS [BPRSd] total, BPRS [BPRSd] core items, CGI-S, CGI-I).

7.3.2 Choice of Dose

In the fifty-two week study 303, all doses (ziprasidone 20 mg bid, 40 mg bid, and 80 mg bid) tested were shown to be efficacious when compared to placebo. However, in study 106, statistical significance was seen in this four week study in the ziprasidone 60 mg bid group, and not in the ziprasidone 20 mg bid group. Study 114 was able to show statistically significant improvement at doses of ziprasidone 40 mg bid and 80 mg bid. The results of study 115 were supportive of efficacy in all doses tested (ziprasidone 20 mg bid, 60 mg bid, and 100 mg bid) at week six. Utilizing results from study 115, the sponsor was able to statistically show a dose response relationship when comparing all doses with placebo; however, the actual numerical differences seen between doses in the efficacy variable scores resembled more of a plateau phenomenon. Therefore, it can not be definitively concluded that increasing the dose clinically would increase the efficacy of this drug.

The drug was administered post-prandial in all studies.

The sponsor has recommended a daily dose of ziprasidone 40 mg bid administered with food. The proposed labeling includes suggestions to increase the dosage to 80 mg bid for some patients and that doses

above 80 mg bid were not shown to be more efficacious than 100 mg bid. This information accurately reflects the findings from these efficacy studies, but the sponsor does not mention that for some patients ziprasidone 20 mg bid proved to be efficacious.

7.3.3. Duration of Treatment

Both six week studies reviewed (114 and 115) demonstrated better efficacy results than the four week studies (106 and 104). It appears that the longer trials of six weeks had a better treatment outcome for psychotic symptoms. The proposed labeling does not address the issue of what time period constitutes a sufficient trial.

Study 303 shows that, after 52 weeks, this drug continues to be effective in the treatment of psychosis. As discussed previously, this trial is not useful with respect to evaluating relapse prevention.

7.4 Conclusions Regarding Efficacy Data

Ziprasidone has been proven to be efficacious in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder in more than one well controlled study. Results of the a year long study have shown that responders of ziprasidone in this trial had fewer psychotic symptoms compared to placebo, but it is unclear if the sponsor's definition of prevention is accurate enough to make a claim of relapse prevention.

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

The sponsor submitted the integrated safety data base of Phase II/III studies and a safety update for review. The electronic submission did not include the ability to manipulate safety data and the review was dependent on the sponsor's compilation of data into tables. The safety update and Integrated Safety Summary (ISS) did not always include needed summary information and a careful review of the text was required. There was some additional information from Japanese studies which was not a part of the integrated safety data base, but is referred to when a serious event emerged. The main focus of the review was on the Phase II/III integrated safety data base to identify significant adverse events. To examine for common adverse events, more emphasis was placed on safety data pooled from the placebo controlled studies which were of similar duration (Studies 104, 106, 114, 115) to allow for comparator control. The only other placebo controlled study was the 52 week study 303 which was examined within the integrated safety data base and provided data on events occurring over a longer period of time.

Amongst the data submitted, there were several subjects listed as being in blinded groups in the safety update; the sponsor was able to reveal the specific treatment group when it was requested. Subjects in blinded groups were included in the calculations of subject years exposure.

There were 2140 subjects exposed to ziprasidone that were included in the original submission (cut-off date 10/31/96); data on an additional 425 subjects taking ziprasidone was in the safety update (cut off date 5/15/97). Therefore, the total integrated safety data base recounted the experience of 2565 psychotic patients who were medicated with ziprasidone. When calculating subject-years exposure, the sponsor chose to include the additional studies Study 120 (for dementia: n=12) and Study 105 (IM ziprasidone: n=11) despite their not being part of the integrated safety data base. Including these additional studies, the exposure time calculated by the sponsor is 772 subject-years based on a total of 2588 subjects. In the 3/20/98 submission, the sponsor submitted a recalculated patient exposure time with a cut-off date of December 31, 1997 based on 2993 subjects which totaled 1189 subject years of exposure to ziprasidone. **For the purposes of this review, the calculation of subjects years exposure will be based on the figure of 772 subject-years (from the safety update of 8/29/97), because the report of December 31, 1997**

did not include safety data for review. Please refer to Section 5.0 for further details of subject exposure information.

Individual subjects will be referred to by their study subject number. This review will omit the first three numbers (128) which denote that the study was conducted in the Pfizer Central Research. Also omitted will be the first zero in each subject number. In the subject number presented, the first three digits indicate the number of the study in which the subject participated. Subjects were reassigned numbers when they entered an extension study; whenever relevant, both numbers will be listed.

8.1.1 Deaths

Please refer to Appendix 8.1.1.1 for a full list of all deaths known to have occurred in subjects ever exposed to ziprasidone. As of the sponsor's cut off date of May 15, 1997 in the safety update, there have been a total of 32 subjects taking ziprasidone who have died; this includes one death (Subject JP-95-601162-02) which occurred in a Japanese study which is not considered part of the integrated safety data base. As of the sponsor's submission of 3/20/98, the sponsor reports that there was a total of 35 deaths as of 12/31/97); however, this submission was not accompanied by any supporting data. Therefore, this review can only discuss **deaths as of 5/15/97**.

Eighteen deaths occurred within 30 days or less of the subjects' discontinuation of ziprasidone, **eight** of them could be considered as sudden unexpected deaths in which the subjects were either found dead or died within 24 hours of onset of their symptoms associated with death. Of these eight deaths, it seems that only **one** case (115-6940394) may be determined to be temporally unrelated to the use of ziprasidone; this subject died 29 days after discontinuing ziprasidone and was being treated with risperidone at the time of death. [Note: the sponsor included an additional sudden unexpected death after the May 15, 1997 cut-off (in 12/31/97 report: submitted 3/20/98), but did not submit any data regarding this death; therefore, this additional sudden death will not be discussed in this review]. **There were no sudden unexpected deaths in the placebo group** in which the subjects were either found dead or died within 24 hours of onset of their symptoms associated with death (the sponsor refers to one sudden unexpected death in the placebo group in the submission of 2/13/98; however, this was unable to be confirmed by review of the safety data base.).

Of the other seven subjects who died suddenly, **two** subjects died of undetermined causes: 1) Subject 304E-1930379, a 52 year old male with schizophrenia died while taking a nap; 2) Subject 108-5920750, a 39 year old female with schizophrenia was found dead with a cause not clearly determined; the sponsor offered speculation regarding her diabetic and alcohol use history to explain this death. The sponsor's CRFs did not include autopsy reports for these subjects.

Three of the subjects who experienced a sudden death were reported on autopsy to have symptoms related to cardiopulmonary systems: 1) Subject 108-6070305 was a 46 year old male with schizophrenia whose death was attributed to acute and chronic asthmatic bronchitis and granulomatous myocarditis, 2) Subject 105-5340021 was a 70 year old female with dementia who died by cardiopulmonary arrest attributed to arteriosclerotic cardiovascular disease, and 3) Subject 116B-5080001 was a 54 year old male with schizophrenia who was found dead in his hospital bed with an autopsy showing COPD, cardiac hypertrophy, and diffuse atherosclerosis.

One subject (302E-3190375), a 48 year old male with schizophrenia was found dead; he had a history of seizures and polydipsia, and exhibited hypertension and tachycardia during his treatment with ziprasidone. An autopsy was not included in the NDA submission.

Subject 308-0350003, a 63 year old male with schizophrenia collapsed in a "lunch club." The cause of death was determined to be a rupture of an abdominal aortic aneurysm and gross diffuse atherosclerosis.

Another subject that deserves mention, although not meeting the definition of SUD, is subject 301-3110977, a 28 year old female with schizophrenia whose death occurred two days after discontinuing ziprasidone. Upon discharge from the study, this subject had ECG changes consistent with subendocardial ischemia with substernal pinching and was transferred to an internal medicine unit. Her death occurred two days later of unknown causes; her treatment regimen at the time of death included thioridazine and nitrazepam. The CRF did not provide more information than the patient summary and did not include any notes regarding this subjects' transfer to the medicine unit.

There were nine subjects whose death occurred within thirty days of discontinuing ziprasidone in which it appeared to be unlikely that their death was related to exposure to ziprasidone. Two subjects (116B-6590001 and 303-1970299) had been on another antipsychotic for more than three weeks after discontinuing ziprasidone. The remaining seven subjects (108-6090381, 116B-6940004, 117-6870317, 117-7060529, 302-2600156, 302E-1590029, JP-95-6011622) were victims of accidents or suicide.

In the ziprasidone treatment group there were a total of four probable suicides occurring within 30 days or less of discontinuing treatment. There was one subject (106-5520126) in the placebo group who committed suicide eight days after completing the study. There were two reports of suicide in the haloperidol group: 1) Subject 108-05820040 who committed suicide six days after discontinuing haloperidol, and 2) Subject 108-5940564 who overdosed while being treated with haloperidol. There were no subjects known to commit suicide during treatment with risperidone. The rate of suicide in 1000 subject-years for subjects in the ziprasidone group was 5.2. In the haloperidol group, the rate was 15 suicides per 1000 subject years; the rate of suicide for the placebo group was 19 suicides per 1000, and placebo group in this data base had a rate of zero. It is recognized that suicide may be a manifestation of the psychiatric disease under study, and this data does not suggest that ziprasidone increases the risk of suicide.

Appendix 8.1.1.2 gives the mortality rates for subjects in Phase II/III trials of the integrated safety data base who have died during the study or within thirty days of discontinuing the studies. In determining subject-years exposure, the sponsor used 5/15/97 as the cut-off date for deaths, while the cut-off date for the denominator determining the subjects years was sometime prior to 5/15/98 (despite requests, the sponsor did not provide the cut-off date for the denominator of the subject years calculation in the Safety Update of 8/29/97). In this data base, the placebo group demonstrates the highest mortality rate.

In Appendix 8.1.1.3, the rate of sudden unexpected death (SUD) is calculated for this NDA data base. The SUDs rate for the ziprasidone group (n=2565) is 9.1 SUD per 1000 subject years , while placebo (n=382) and haloperidol (n=585) groups had zero and the risperidone group (n=295) had a 9.5 SUD per 1000 rate. It would appear that ziprasidone and risperidone have a similar SUD rate within this data base; it is noted, however, that the risperidone rate is based on a sample size roughly one-tenth the size of the ziprasidone data base and that the SUD rate is based upon one death (due to acute aspiration).

Appendix 8.1.1.4 provides a comparison of the SUD rate of the most recent antipsychotic NDAs submitted to FDA; for ziprasidone, the information is based on the data base discussed in this review, while the other information has been obtained from the document: Review of Clinical Data: *General Characteristics of the Deaths in the NDAs for Olanzapine, Risperidone, Quetiapine and Sertindole* by Greg Burkhart, M.D. (HFD-120: 3/3/98). From this table, it appears that both ziprasidone and sertindole surpass the SUD rate of olanzapine, risperidone, and quetiapine.

In his report Review of Data Quality, Coding, All Cause Mortality and Sudden Deaths (HFD-120: 2/3/98), Dr. Boehm concludes that the SUD rate found in the ziprasidone NDA data base is 6 times higher than the SUD rate from a pool of combined data of recently approved antipsychotic NDAs.

8.1.2 Other Serious Adverse Events

The sponsor did not define a serious adverse event in the Integrated Summary of Safety (ISS). A review of the pivotal study protocols revealed that Pfizer applied the same definition for a serious adverse event that is used by FDA (i.e. any drug experience that is fatal or life-threatening, is permanently disabling, requires hospitalization, or is a congenital anomaly, cancer, or overdose). These protocols included requests that any serious adverse event be immediately reported to Pfizer. Serious adverse events were submitted as listings itemized by subjects and COSTART body system/preferred term.

There were no serious adverse events reported in the Phase I ziprasidone studies. The original submission stated that within the primary safety data base, 261 subjects (12.2%) of the 2140 subjects treated with ziprasidone experienced serious adverse events in Phase II/III studies. Based on a count of the line listings submitted in the update (the sponsor did not provide a summary table of adverse events in the safety update), 115 additional subjects appeared to experience serious adverse events; therefore, 376 subjects (14.7%).of the total 2,565 subjects exposed to ziprasidone in Phase II/III studies of the integrated safety data base experienced a serious adverse event . The sponsor may have presented a single serious adverse event under two or three COSTART terms. It is noted that some individual subjects experienced more than one serious adverse event during these trials.

Appendix 8.1.2 lists serious adverse events considered to be common events in the patient population studied or for which there is not sufficient evidence to state that they were drug related. Any event which occurred greater than 30 days after the study drug was discontinued will not be discussed in this review; in the NDA submission, the sponsor included these events which occurred greater than 30 days after the study drug was discontinued. There were several instances in the sponsor's tables in which individual events may have been listed under two or three COSTART terms; in most cases, this review will present them as a single event in only one body system below. Also, there were some instances in which this reviewer felt that alternative COSTART terms reflected the adverse event more accurately than the sponsor's choice of category; the cases which have been recategorized in this review are discussed in section 8.1.5.2. (Note: fatal cases will not be repeated in this section.) .

8.1.2.1 Syncope/Hypotension

Because of ziprasidone's alpha adrenergic properties, it not unexpected that orthostatic hypotension and syncope would be present as an adverse event. There were 5 syncopal events and one hypotensive event that were considered to be serious adverse events. It is unclear what criteria the sponsor used to report a syncopal event as a serious event, as syncope was observed in 0.7 % (15/2140) of the subjects in the phase II/III safety data base (cutoff 10/31/96) , while hypotension (combining postural hypotension and hypotension) occurred in 2.5 % (53/2140) of subjects in the phase II/III safety data base. For the sake of completeness, in the phase I studies, there were 14 subjects who experienced a syncopal episode of which four experienced a second episode upon rechallenge of ziprasidone. There were at least thirteen episodes of syncope [102-5130005, 102-5140005, , 114-6170217, 116B-5980001, 116B-6940002, 117-6870313, 303-0570124, 303-0710101, 303-2650321, 303-2120222 (source: line listing in Appendix VI table 1b of sponsor's submission) and 108-6050002, 108E-5550096, 108E-5780052 (source: safety narratives)] in the Phase II/III data base that were not reported by the sponsor as a serious adverse event. The following table summarizes the subjects who where determined to have syncope/hypotension as a serious adverse events:

Syncope and Hypotension listed as a serious event in subjects taking ziprasidone

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	DAYS OF TREAT-MENT	SERIOUS ADVERSE EVENT/ COMMENTS
102-5130005	62/M	40	20	Subject fell, breaking left lateral malleolus and ziprasidone was discontinued. 24 hours later, subject had two episodes (10 sec.) of loss of consciousness. Etiology was not determined.
116B-5900002	31/M	160	82	Subject was on ziprasidone when he fell backwards with loss of consciousness while smoking a cigarette. Subject reported headache the night before and dizziness prior to fall. Etiology of syncope was unclear
118-7090001	44/M	40	4	Subject fell backwards and was found to be hypotensive (70/50); incident attributed to orthostatic hypotension. One day after his last ziprasidone dose, subject was found on the floor unresponsive. He was found to have a sodium level of 120 (but his baseline was 127) and he was placed on fluid restriction. EEG and CAT scan were benign. No cardiac work up was done.
116B-5510003	32/M	80	43	On the same day that subject experienced syncopal episode, he developed a rash and edema in the regions of the lips, left hand and ankles. ECG showed sinus bradycardia of 52 bpm otherwise it was normal. Case also included in rashes.
116B-5230001	41/M	80		Case report form suggests that the syncopal event occurred because the subject had not eaten for a couple of days, but emergency work up was not located in the CRF.
SUBJECT #	**AGE/ SEX**	**MODAL DOSE (MG/D)**	**DAYS OF TREAT-MENT**	**SERIOUS ADVERSE EVENT/ COMMENTS**
Hypotension				
303-0710098	59/M	40	4	Hypotension (95/70), vomiting, hypotension, sweating, pallor, dypsnea (h/o diabetes) ECG at baseline: QRS:80, PR:160, QT:346, QTc: 447, rate:100 bpm ECG at incident (according to CRF): QRS:90, QT:326, QTc:473, rate: 123 bpm. with flat t-wave and arrhythmia.

8.1.2.2 Rash

There were 21 subjects who discontinued for rashes in the originally submitted integrated safety data base; the haloperidol group only had 2 withdrawals, while the placebo group had 1 withdrawal. It was left to the investigator's discretion as to whether or not an event was reported as serious, and there did not appear to

be any consistent feature that merited reporting a rash as a serious event. The following table lists the subjects whose rashes were considered serious adverse events.

Subjects with rash as a serious adverse event

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	DAYS OF TREAT-MENT	SERIOUS ADVERSE EVENT/ COMMENTS
106-5520124	41/M	40	15	"Facial rash" developed 9 days after starting ziprasidone. Discontinued due to rash at day 15: diagnosis of sebaceous dermatitis on face arms, thighs, and legs. Subject also had hypertension with blood pressure of 148/112.
106-5520047	46/F	120	29	Raised rash on lips, arms, back and buttocks with pruritis. Biopsy showed superficial perivasculitis with extensive edema and eosinophilia. Treated with antihistamines.
115-6560036	48/M	200	40	Severe generalized rash with itching mostly on the chest and upper extremities. Hospitalized to rule-out Stevens-Johnson Syndrome. Treated with benedryl and calamine lotion. Improvement noted within 2 days of discontinuing ziprasidone.
115-6890088	55/M	120	37	Generalized urticaria. Resolution within 5 days. Treated with prednisone, hydroxizine, and diphenhydramine.
301-0720148*	54/F	200	33	Urticaria and itching
116B-5510003	32/M	80	43	Syncope accompanied by a rash and edema in the regions of the lips, left hand and ankles. ECG showed sinus bradycardia of 52 bpm otherwise it was normal. Possible angioedema.

*Safety Update

As noted above, there were three subjects who discontinued from the study whose hospitalization was extended because of the symptoms of rash. Rash was the most common adverse event resulting in withdrawal from the ziprasidone treatment groups (see 8.1.3.2). A review of the NDA safety data base revealed that there were several subjects whose rash was accompanied by an elevated white blood count, and at least two subjects with rash whose eosinophil count was elevated. Most cases of rash resolved within one week of discontinuing ziprasidone; one subject (117-5130506) experienced "bullous drug eruptions/ pruritic blisters with post-excoriated papules" on the hands, wrist, scalp, and neck which resolved 24 days after discontinuing ziprasidone. Medications used to treat rashes included steriods (oral and topical) and antihistamines. Three subjects (115-6560036, 106-5520047, and 115-6890088) required hospitalization for observation of their rashes.

8.1.2.3 Elevated Transaminase

It is unclear how the sponsor determined whether or not a laboratory value was considered a serious adverse event; therefore, the reader is referred to section 8.1.6.3 for a listing of subjects who withdrew from studies because of an abnormal laboratory values.

Abnormal transaminase values listed as serious adverse events

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	DAYS OF TREAT-MENT	SERIOUS ADVERSE EVENT/ COMMENTS
104-5310185	38/M	40	7	Increased ALT and AST at first lab test after starting ziprasidone with peak five weeks (normal at baseline.). This subject was diagnosed with Hepatitis C diagnosed six months after discontinuing ziprasidone. There was a temporal relationship of the elevated LFTs and the initiation of ziprasidone .
106-5390092	35/M	120	9	ALT:165, AST:89U/L. After stopping ziprasidone, ALT returned to normal in 5 days and AST returned to normal in 19 days.
104-5360293	56/F	80	28	Elevated LDH (peak 419)
117-6390290	21/M	80	72	ALT: 133 U/L; AST: 43 U/L LFTs returned to normalized after discontinuing ziprasidone.

8.1.2.4 Neuroleptic Malignant Syndrome

The sponsor did not identify any episodes of neuroleptic malignant syndrome (NMS) in this submission. However, upon review of the case histories, it appeared that there was one 51 year old male subject (109-5650041) who presented classic symptoms of NMS, and a 40 year old female who had symptoms which may have been also been a manifestation of NMS. The following table summarizes these two cases:

Serious events manifesting symptoms of NMS

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	DAYS OF TREAT-MENT	SERIOUS ADVERSE EVENT/ COMMENTS
109-5650041	51/M	80	3	Became confused with temperature of 99.9 ° F, creatinine kinase of 955, and sinus tachycardia. Within two weeks of discontinuing ziprasidone, the CPK levels normalized and the tachycardia resolved within 3 days of ziprasidone discontinuation.
116B-5530001	40/F	120	830	Episode of odd and confused behavior, a temperature of 101° F, diaphoresis, bradycardia, urinary incontinence and CPK level of 944 U/L. Her husband reported that she had similar episodes in the past. Urine culture showed E. coli infection. The sponsor chose to categorize this serious episode as UTI.

8.1.2.5 Extrapyramidal Symptoms

The following table delineates episodes of extrapyramidal symptoms which were considered serious adverse events.

Serious adverse events of extrapyramidal symptoms

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	DAYS OF TREAT-MENT	SERIOUS ADVERSE EVENT/ COMMENTS
109-5670019	39/M	160	23	Discontinued with ziprasidone due to severe akathisia.
115-6940394	43/M	40	16	Developed tardive dyskinesia 3 days after stopping ziprasidone and was on risperidone at the time of the incident.
116B-06820005	52/M	120	81	Parkinsonism, restlessness and insomnia Subject took 200 mg qd x 2 weeks and was considered as an overdose.
303-1970265	68/M	40	7	Case report form listed him as having "worsening of vital functions" and was later clarified to be severe extrapyramidal symptoms (asthenia), general weakness, dehydration, hypotension, hypersalivaion. This subject was categorized by the sponsor as having hypotension as a serious adverse event when in fact his blood pressure was consistently low (approximately 90/50) for the duration of the study as well as at baseline.
303-2000113	35/F	40	13	Acute dystonia.
In combination with haloperidol				
116B-05530002	62/F	200	137	Severe akathisia in combination with haloperidol .
301E-12106661	35/M	80	43	Severe generalized dystonia 1 day after stopping ziprasidone. Subject was given one dose of haloperidol prior to episode

8.1.2.6 Aspiration Pneumonia

Because aspiration pneumonia has been associated with neuroleptic use, the following cases are listed as possibly related to ziprasidone use:

Cases of pneumonia

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	LENGTH OF TREAT-MENT (DAYS)	SERIOUS ADVERSE EVENT/ COMMENTS
105-5340003	98/F	6	59	Subject had cough, rales, episode of vomiting and temperature of 100.8 ° F and was admitted to the hospital for aspiration pneumonia
116B-7010012	47/M	160	321	Hospitalized x 2 days for pneumonia.

8.1.2.7 Seizures

In the safety update (submitted 8/29/97), the sponsor reported the seizure rate to be 1.8 subjects per 100 subject years (12/772) or 0.54 % (12/2588) of the subjects in the NDA data base experienced a seizure while taking ziprasidone. The original NDA submission (3/18/97) includes six subjects who discontinued as a result of their seizure or possible seizure activity. The safety update did not include specific subject information.

The occurrences of seizure reported in the original submission is summarized in the tables below; seizures occurring beyond 6 days of treatment were not included. The first table is a summary of the subjects who experienced seizures within the original NDA submission of 3/18/97. The second table summarizes only subjects who discontinued because of an episode of seizure activity as of the safety update of 8/29/97. Information was obtained from the sponsor's ISS, patient narratives in the original NDA submission and the safety update of 8/29/97.

Summary of seizures with ziprasidone treatment in the original NDA data base (cut-off 10/31/96)

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	LENGTH OF TREAT-MENT (DAYS)	ADVERSE EVENT/ COMMENTS
108-5880461	45/M	80-120	22	Complex partial seizure. Treated with phenytoin and lorazepam. No h/o seizure.
108E-6060082/ 108-6060053	44/M	Unclear	9 months	Listed as possible seizure. Unresponsive when brought to the hospital. MRI was normal except for sinusitis; blood gas was pH 7.35, pCO_2=59, pO_2=50, HCO_3=33, Na=133, and WBC=20D/micro. Subject became alert within first hour and according to the patient summary was discharged with phenytoin and abuterol nebulizer. He was hospitalized two days later for further evaluation as he was febrile and had labored breathing requiring intensive care unit and corticosteroids.
116B-5900002 (also listed as syncope)	31/M	160	82	Listed as possible seizure. Subject was on ziprasidone when he fell backwards with loss of consciousness while smoking a cigarette. Subject reported headache the night before and dizziness prior to fall. Some limb movement occurred during episode.
301-2170651	31/M	120	45	Convulsive crisis on day 3.
303-0570124	35/M	40	364	Listed as possible seizure. Subject was found unconscious in the hospital ward; no abnormalities found in EEG and ECG showed "some tachycardia" up to nine days following the episode. (Note: there was no CRF available and no specific information regarding the work up of this episode). Subject completed the study for about two more weeks with metoprolol added to his medication regimen. One month after stopping ziprasidone, subject had a seizure. No prior h/o seizure.
303-1780041	45/M	40	2	Grand mal seizure. Treated with lorazepam.

Summary of seizures with ziprasidone (con't)				
SUBJECT #	**AGE/ SEX**	**MODAL DOSE (MG/D)**	**LENGTH OF TREAT-MENT (DAYS)**	**ADVERSE EVENT/ COMMENTS**
303-2380193	49/M	40	183	Grand mal seizure on day 122. Treated with diazepam.
303-2650327	60/F	40	365	Tonic clonic seizure on day 153.

Discontinuations due to seizures in the safety update of 8/29/98 (cut-off 5/15/97)

SUBJECT #	**AGE/ SEX**	**MODAL DOSE (MG/D)**	**LENGTH OF TREAT-MENT (DAYS)**	**ADVERSE EVENT/ COMMENTS**
302E-3570475*	41/F	Unclear	7	Generalized seizure. No h/o seizure.
306E-3740017*	26/M	80	42	Tonic-clonic seizure. Treated with diazepam. H/o febrile seizure in childhood. No h/o seizure in adolescents and adulthood.
307-3770251*	36/M	40	14	Grand mal seizure. No h/o seizure.
JP-95-601 23-01*$^{\Delta}$	61/M		9	Epileptic seizure. Treated with diazepam and carbamazepine. H/o one prior seizure 2° to polydipsia.

*From Safety Update

$^{\Delta}$Not in the integrated safety data base

8.1.3 Dropouts and "Other Significant Adverse Events"

8.1.3.1 Overall Profile of Dropouts

According to the original submission, the primary integrated database included 1263 subjects (59%) of the total 2140 who prematurely discontinued treatment in Phase II/III trials. The sponsor did not provide summary data of the discontinuations in the safety update, but a count of the line listings showed that there were 72 new discontinuations. The sponsor's table below provides reasons for discontinuations for the original submission. Please note that this table does not include data from the safety update.

Insufficient clinical response was the reason that the majority of discontinuations occurred for the open label and placebo controlled trials. The sponsor's table below compiles the reason for discontinuations in four of the pivotal short term studies where a placebo comparison can be observed:

Overview of Phase II/III Study Discontinuations
All Oral Dosing Phase II/III Studies

Number (%) of Subjects	Ziprasidone 2140	Haloperidol 407	Risperidone 296	Amisulpride 19	Placebo 354
Discontinuations					
Adverse event	226 (10.6)	64 (15.7)	23 (11.2)	0	18 (5.1)
Insufficient clinical response	609 (28.5)	60 (14.7)	29 (14.1)	1 (5.3)	143 (40.4)
Laboratory findings	16 (0.7)	2 (0.5)	3 (1.5)	0	1 (0.3)
Special safety test finding	2 (0.1)	0	0	0	1 (0.3)
Patient died	3 (0.1)	1 (0.2)	1 (0.5)	0	0
Other	452 (21.1)	82 (20.1)	37 (18.0)	2 (10.6)	57 (16.1)
Total	1308 (61.1)	209 (51.4)	93 (45.1)	3 (15.8)	220 (62.1)

Other reasons for discontinuation may include failure to meet randomization criteria, lost to follow-up, protocol violation, withdrawn consent, etc.
Includes duplicate counting of 45 Ziprasidone subjects who discontinued both the parent and extension study.
Protocols: 015,101,102,104,104E,106,106E,108,108E,109,109E,110,111,114,115,116B,117,118,122,301,302,303,304,305

Insufficient clinical response was the reason that the majority of discontinuations occurred for the open label and placebo controlled trials. The sponsor's table below compiles the reason for discontinuations in four of the pivotal short term studies where a placebo comparison can be observed:

Overview of Phase II/III Study Discontinuations
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies

Number (%) of Subjects	Ziprasidone 702	Haloperidol 85	Placebo 273
Discontinuations			
Adverse event	29 (4.1)	7 (8.2)	6 (2.2)
Insufficient clinical response	165 (23.5)	13 (15.3)	95 (34.8)
Laboratory findings	4 (0.6)	0	0
Other	118 (16.8)	17 (20.0)	49 (17.9)
Total	316 (45.0)	37 (43.5)	150 (54.9)

Other reasons for discontinuation may include failure to meet randomization criteria, lost to follow-up, protocol violation, withdrawn consent, etc.
Protocols: 104,106,114,115

As seen above, there was a higher withdrawal rate for insufficient efficacy in the placebo group than in the ziprasidone group; however, the drop out rate for adverse events was higher for the groups receiving ziprasidone.

8.1.3.2 Adverse Events Associated with Dropout

In the integrated safety data base (excluding data from the safety update), 221 subjects (10.3 %) of the 2,140 subjects exposed to ziprasidone discontinued the study due to an adverse event.

In order to establish a comparator control, it is most helpful to focus on data collected from placebo-controlled studies. The following table lists the adverse events which resulted in 2 or more withdrawals from the placebo-controlled pivotal studies (including studies 104, 106, 114, and 115):

Adverse events leading to discontinuations in short term placebo-controlled studies 104, 106, 114, 115

	Ziprasidone n=702	Placebo n=273	Haloperidol n=85
Total # of subjects discontinuing due to adverse events (%)	29 (4.1)	6 (2.2)	7 (8.2)
ADVERSE EVENT			
Rash	7 (1.0)	0	0
Nausea	3 (0.4)	1 (0.4)	0

Adverse events leading to discontinuations in short term placebo-controlled studies 104, 106, 114, 115 (con't)

	Ziprasidone n=702	Placebo n=273	Haloperidol n=85
Hypertension	2 (0.3)	0	0
Tachycardia	2 (0.3)	0	0
Vomiting	2 (0.3)	0	0
Akathisia	2 (0.3)	0	2 (2.4)
Hostility	2 (0.3)	0	0
Insomnia	2 (0.3)	0	0
Somnolence	2 (0.3)	0	1
LFT abnormality	2 (0.3)	0	0

NOTE: It appears from the sponsor's data that individual subjects may have experienced more than one adverse event.

8.1.4 Other Search Strategies

None.

8.1.5 Common Adverse Events

8.1.5.1 Approach to Eliciting Adverse Events in the Development Program

Pfizer did not provide their working definition of an adverse event in the Integrated Summary of Safety. All adverse events presented were classified by organ system using COSTART terminology. The sponsor stated that adverse events were collected by either direct observation by the investigator or by patients volunteering this information. This method may result in an under representation of adverse events, because the schizophrenic population may not be able to spontaneously volunteer and articulate their discomfort.

The sponsor states in the Integrated Summary of Safety (ISS) that investigators categorized adverse events as to whether or not there was a probable relationship to the study medication. The ISS presented tables which addressed events that were judged by the investigators to be related or of unknown relationship to the treatment medication; however, the sponsor stated that all causality tables included all adverse events independent of the investigator's judgment (submitted 4/9/98).

8.1.5.2 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

The sponsor reports using the COSTART dictionary, coding adverse events by body system and preferred terms. In most cases, the sponsor chose appropriate categories; however, there were several cases in which alternative categories were chosen by this reviewer to better reflect the clinical presentation as described in the patient profiles and case report forms. Serious adverse events and discontinuations which have been recategorized from the sponsor's original COSTART TERMS are as follows:

1. Subject 116B-553001: a 40 year old female who was taking 60 mg of ziprasidone daily for 830 days began to have an episode of odd and confused behavior, a temperature of 101° F, diaphoresis, bradycardia, urinary incontinence and a CPK level of 944 U/L. Her husband reported that she had had similar episodes in the past. Her urine culture showed an E. coli infection. The sponsor chose to categorize this serious episode as UTI; to be more accurate, it needs to be considered that this case may also have been a manifestation of neuroleptic malignant syndrome.

2. Subject 118-7090001: a 44 year old male who was taking 40 mg ziprasidone daily for 4 days, fell flat backwards 3 ½ hours after his last dose and was found to be hypotensive (70/50). One day after the last

ziprasidone dose, this subject was found on the floor unresponsive; he was found to have a sodium level of 120 (but his baseline was 127) and was re-hospitalized and placed on fluid restriction. EEG and CAT scan were benign. No cardiac work up was done. The sponsor chose to categorize this as a seizure despite that there was no seizure witnessed; therefore, this was recategorized as syncope.

3. Subject 101-5060084: a 52 year old male who was taking 20 mg ziprasidone daily for 4 days was found at home confused and fluid depleted secondary to hyponatremia with sodium level of 111. He was admitted to the hospital and with fluid restriction, and his sodium returned to normal. This was originally cataloged as confusion and this reviewer reclassified it as hyponatremia.

4. Subject 303-0212105: a 56 year old male who was taking 160 mg ziprasidone daily for 280 days who reportedly had a history of essential hypertension (but was normo-tensive throughout the study), fell down the steps, lost consciousness and was noted to have a blood pressure of 220/140. This case was listed as intracranial hemorrhage which actually occurred as a result of this fall; it was recategorized as a hypertensive episode because this event appeared to have preceded the fall.

The following adverse events were listed under reasons for discontinuations, but have been considered to be serious events by this reviewer:

1. Subject 109-5650041: a 51(age was listed as 48 in the summary, but CRF stated 51) year old male who, within the first few days of treatment with ziprasidone 20 mg qid, became confused with a temperature of 99.9 ° F, a creatinine kinase level of 955, and sinus tachycardia. Within two weeks of discontinuing ziprasidone, the creatinine kinase levels normalized and the tachycardia resolved within 3 days of ziprasidone discontinuation. The sponsor did not list this as a serious adverse event; but as a case of discontinuation due to the event of tachycardia. The presented data more accurately suggests that this was a serious adverse event of probable neuroleptic malignant syndrome.

2. Subject 116B-5230001: a 41 year old male who was taking 80 mg ziprasidone for 80 days experienced mild nausea and an episode of syncope and was taken to the emergency room. The sponsor categorized this as a discontinuation and did not list this as a serious adverse event; the case report form had a notation from the investigator that the emergency room physician thought that this event was due to not eating for a couple of days; however, the work up was not included in this submission. It was felt by this reviewer that this syncopal event should be classified as a serious adverse event.

3. Subject 104-5220146: a 45 year old female (taking 80 mg ziprasidone x 12 days) with a history of hypertension stabilized with nifedipine was hospitalized for a possible hypertensive crisis with a diastolic pressure up to 120. This adverse event was listed in the discontinuations by the sponsor. It is the opinion of this reviewer that this adverse event should be reclassified as a serious adverse event as this event resulted in the subject's being hospitalized.

8.1.5.3 Selecting the Best Adverse Event Tables for Characterizing the Adverse Event Profile

A helpful perspective in the attempt to determine the occurrence of events related to the study medication is to look at incidents of adverse events in placebo-controlled trials. Appendix 8.1.5.3 consists of the sponsor's table of adverse events occurring in 1 % of the subjects taking ziprasidone in the data collected from the placebo-controlled pivotal studies (104, 106, 114, and 115). The proposed labeling include a 1 % table based on this data. Events occurring in this pooled data that are not listed in the proposed labeling are anxiety, tremor, conjunctivitis, and urinary incontinence; these events were seen with equal frequency in the placebo group.

Appendix 8.1.5.4 is extracted from the sponsor's proposed labeling and lists all adverse events occurring in the primary safety data base in the original submission; data from the safety update is not included in this summary.

8.1.5.4 Identifying Common and Drug-Related Adverse Events

Common events were determined by identifying events which occurred in at least 5% of the ziprasidone group and occurred more than twice as frequently in the ziprasidone than in the placebo group. The drug related adverse events fulfilling this criteria were extrapyramidal syndrome and somnolence as seen in the 1% table. Weight gain was observed in 10 % (61/622) of subjects taking ziprasidone in the short term placebo controlled phase II/III studies versus 4 % (9/227) in placebo (see Appendix 8.1.7.3.2); it is noted that weight gain was omitted from the 1% table.

8.1.5.5 Additional Analyses and Explorations

Dose Response

A dose relationship for several adverse events was established when the sponsor applied the Mantel-Haenszel test to the pooled data from pivotal short term studies (104, 106, 114, 115) for doses of <40 mg bid, 40 mg bid, 80 mg bid, and ≤ 100 mg bid. The sponsor's analysis showed a statistically significant dose relationship ($p \leq 0.05$) with the following adverse events: asthenia, postural hypotension, anorexia, diarrhea, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, respiratory tract infection, rhinitis, rash (p=0.051), abnormal vision.

Demographic Analyses

The interaction effect of gender, age, or race was determined in the common adverse events that occurred at least 5% in the ziprasidone group and more than twice as frequently than in the placebo group. The sponsor states that using the Breslow-Day Odds Ratio, there was no differences noted in the incidence of somnolence (the only adverse event analyzed) when examining gender (p=0.89), age (p=0.62) or race (p=0.89).

The demographics for this analysis is as follows:

Gender
Women: n=186 ziprasidone, n=71 placebo
Men: n=516 ziprasidone, n=12 placebo

Age
18-64 y.o.: n=693 ziprasidone, n=271 placebo
65-74 y.o.: n=9 ziprasidone, n=2 placebo

Race
Caucasian: n=462 ziprasidone, n=171 placebo
African American: n=175 ziprasidone, n=68 placebo
Asian: n=21 ziprasidone, n=2 placebo
Other: n-44 ziprasidone, n=26 placebo

8.1.6 Laboratory Findings

8.1.6.1 Extent of Laboratory Testing in the Development Program

The review of laboratory findings encompass data from the Phase II/III trials in the integrated safety data base of the original NDA submission. The Integrated Summary of Safety states that routine laboratory tests for all studies included complete blood count, electrolytes, serum hepatic and renal function. The final samples were collected up to six days after the last day of study medication. The frequency of laboratory testing varied amongst the studies; the ISS merely states that routine laboratory tests were collected at baseline and repeated during and/or at the end of the study.

8.1.6.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

This section of the review will concentrate on the pooled clinical laboratory values from the short term placebo-controlled studies 104, 106, 114, 115. This allows for comparison to be made to the placebo group and also may eliminate any confounding variable of time period as the duration of these studies is comparable (studies 104 and 106: 4 weeks; studies 114 and 115: 6 weeks). Laboratory values were collected at different intervals for these studies: 106 and 104 had weekly monitoring, while 114 and 115 had laboratory monitoring about every other week.

8.1.6.3 Standard Analyses and Explorations of Laboratory Data

8.1.6.3.1 Analyses focused on Measures of Central Tendency

The mean change from baseline of clinical laboratory values for ziprasidone and placebo can be found in Appendix 8.1.6.3.1. The sponsor performed the Kruskal-Wallis test using the RANK and ANOVA procedures with an alpha level of 0.05 to analyze the data; it is inferred from the sponsor's table in Appendix 8.1.6.3.1 that there were no statistically significant findings when comparing the ziprasidone group with the placebo group. Inspection showed that the mean changes of note in the ziprasidone group compared to placebo were values for blood urea nitrogen (↓8 %), bicarbonate (↑4.5%), and LDH (↑3%). It is important to keep in mind that the last observation value could be obtained up to six days after discontinuation from the study.

8.1.6.3.2 Analyses focused on Outliers

The sponsor used an elaborate system to determine when a laboratory value had clinical significance; this was not clearly explained in the original NDA submission and a request for further details was made (please refer to submissions of 11/18/97 and 12/17/97). Appendix 8.1.6.3.2a contains the sponsor's laboratory reference ranges used to determine whether the baseline value was normal or abnormal; baseline values were then compared to the worst laboratory value found during the study. The sponsor applied different criteria for subjects who began the study with abnormal laboratory values. Clinical significance was determined using the values in column "A" and "B" in Appendix 8.1.6.3.2b; for subjects with normal baseline values, the worst value was required to be outside the range specified by column "A". Meanwhile, for subjects with an abnormal baseline value it was required that their worst lab value be described by both column "A" and "B" in order to be considered of clinical significance and be included in the number of subjects with laboratory abnormalities.

For reasons explained above, the focus of this section will be the short term placebo controlled trials. Please refer to Appendix 8.1.6.3.2c for the incidence of clinically significant laboratory tests in the short term placebo controlled fixed dose studies 104, 106, 114, 115. Using a Fisher Exact 2-tailed test at the 0.05 alpha level, the sponsor found that statistical significance was seen in the following laboratory values: cholesterol (ziprasidone: 2% versus placebo: 0%) and triglycerides (ziprasidone: 12% versus placebo: 7%).

8.1.6.3.3 Dropouts for Laboratory Abnormalities

Of the 2140 ziprasidone subjects in the phase II/III trials in the original integrated safety data base, the following laboratory abnormalities resulted in early termination in 0.1% or greater of the subjects:

ALT elevation	0.5%
AST elevation	0.4%
Alkaline Phosphatase elevation	0.1%

A criteria to determine when a subject should withdraw from the study was not located in this submission. The following table is composed of subjects who did drop out because of laboratory abnormalities. Information for this table was generated from both the original submission and the safety update which encompasses a total of 2565 subjects exposed to ziprasidone in the Phase II/III data base.

Dropouts for laboratory abnormalities

Subject ID #	Age/Sex	Dose/duration	Most extreme levels	Outcome/comments
Abnormal liver enzymes				
117-6550327	58/M	120 mg 37 days	ALT:156,AST:68 U/L AP:250, GGT:1372 Bilirubin: 2.3mg/dl	Jaundice which resolved two weeks after d/c. Five days after d/c labs began to normalized, but remained elevated.
301-2790615*	43/M	120 mg 42 days	ALT:104,AST:217 U/L	Jaundice, mild, with fever and fatigue. Follow up labs reported to be normal.
#117-622-0033	36/M	160 mg 219 days	ALT:58,AST:158, LD:354 IU/L	LFTs reported to be resolved one day after d/c
117-622-0033	36/M	160 mg 219 days	ALT:58,AST:158, LD:354 IU/L	LFTs reported to be resolved one day after d/c
115-6380055	40/M	120 mg 10 days	ALT:116,AST:188 IU/L	LFTs resolved within two days after d/c
116B-6220001	27/M	200 mg 117 days	ALT:77,AST:144 IU/L	LFTs normalized within one month after d/c
106-5390092	35/M	120 mg 9 days	ALT:165,AST:89U/L	ALT returned to normal in 5 days and AST returned to normal in 19 days. LFTs normalized within five days after d/c
109-5720028	34/F	80 mg 9 days	ALT:128,AST:55 U/L	LFTs normalized within eleven days after d/c
101-5090050	37/M	10 mg 7 days	ALT:56,GGT:137 U/L	Within two weeks, ALT normalized and GGT was returning to normal
101-5050065	39/M	40 mg 8 days	ALT:94,AST:197, GGT:128 U/L	LFTs were lowering within 5 days; no other f/u provided
115-6530148	42/M	120 mg 26 days	ALT:194,AST:80 U/L	LFTs were lowering within 8 days; no other f/u provided
116B-5810013*	43/M	200 mg 171 days	AP: 257 U/L	Subject remained in study and elevated AP did not resolve by the end of the study.
114-5290079**	40/M	80 mg 15 days	AST:377 IU/L ALT:582 LDH:784	Labs returned to normal within one month after stopping ziprasidone
304-1890367	27/M	15 days dose not provided	AST: 111 U/L ALT: 290 U/L	Subject was listed in the safety update as participating in the blinded group with laboratory test abnormalities and **possible hepatitis**. Sponsor revealed that subject was in ziprasidone group. Doses unclear.

Hematologic abnormalities				
303-1800061	65/M	80 mg 89 days	Platelets:12x 10^9/L (nl:160-350)	Value at baseline was 93 x 1 Thrombocytopenia resolved days of d/c.
104-5370243	37/M	40 mg 20 days	Neutrophils: 27 % (1242/UL)	Mild neutropenia resolved wi day of d/c
303-265-0357	36/M	160 mg 41 days	Eosin: 35.1%	Within two weeks after d/c, eosinophilia resolved .
Dropouts for laboratory abnormalities (con't)				
Subject ID #	Age/Sex	Dose/duration	Most extreme levels	Outcome/comments
Abnormal liver enzymes/hematologic abnormality				
303-02710228	54/M	160mg 87 days	ALT:70,AST:85 U/L Prolactin: 0.53 IU/L Hb/Hct:7.1/0.35	Accompanying symptoms of heartburn and epigastric pain were resolved within four weeks of discontinuation and treatment. Subject diagnosed with chronic gastritis by endoscopy and Helicobacter pylori infection. Follow up labs not included in submission.
Glucose abnormality				
117-05130512	35/M	120 mg 194 days	Glucose: 883 mg/DL	Diabetic ketoacidosis successfully treated with insulin. Subject had one previous episode.

*From Safety Update

**Not included in sponsor's calculations (Sponsor listed this subject as discontinuation due to insufficient clinical response

As can been seen from the table above, there were several subjects whose liver function studies elevated while on ziprasidone and the pattern of resolution suggests that these episodes were drug related. Two subjects were reported to exhibit symptoms of jaundice with elevated liver functions tests: one subject (117-6550327) had an extremely high level of GGT (1372 IU/L); the other subject (301-2790615) also had symptoms of fever, and fatigue.

Also of note is the one subject (303-01800061) who withdrew because of thrombocytopenia which resolved upon withdraw from ziprasidone. It is possible that this adverse event may have been drug related.

8.1.6.4 Additional Analyses and Explorations

Prolactin studies were monitored in only two subjects in the short-term placebo controlled studies, one of which was found to have abnormal values. Therefore, it is necessary to look at the total pool of oral dosing phase II/III studies; clinically significant abnormalities were identified in 20% of the (148/741) ziprasidone subjects whose prolactin levels were monitored (see Appendix 8.1.6.4). Using the Fisher two tailed statistical test with an alpha level of 0.05, the sponsor determined that this rate of prolactin abnormality was statistically significant when compared with the placebo subjects monitored.

Thyroid function studies were not tested at all in the short-term placebo controlled studies. In referring to Appendix 8.1.6.4, it can be seen that there were only 224 subjects tested for thyroid functions and when compared to the rate of abnormal findings in the 56 placebo group monitored, there was no statistical significance identified.

8.1.7 Vital Signs

8.1.7.1 Extent of Vital Sign Testing in the Development Program

The ISS does not specify which vital signs were included in each study, nor does it state the frequency of vital sign monitoring; the final vital sign monitoring could occur up to six days after the last dose of study medication was given. The sponsor analyzed changes in standing or sitting systolic or diastolic blood pressure and sitting or standing heart rate, and weight gain or loss. Please refer to Appendix 8.1.7.3.2 for vital sign parameters used to determine clinical significance. There is no data comparing changes of supine and standing vital signs; therefore, orthostatic changes could not be adequately assessed.

8.1.7.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The focus of this section will be on the short-term placebo controlled trials to allow for placebo comparison.

8.1.7.3 Standard Analyses and Explorations of Vital Sign Data

8.1.7.3.1 Analyses Focused on Measures of Central Tendency

Appendix 8.1.7.3.1 contains the sponsor's summary of the median change from baseline to last observation of vital signs. Using the Kruskal-Wallis test with an alpha level of 0.05, the sponsor found a statistically significant change for weight increase (61 of 622 subjects) when comparing the ziprasidone and placebo groups. From these findings, it does not appear that there are significant changes in heart rate or blood pressure reading when comparing placebo and ziprasidone; however, it must be kept in mind that the final reading could have occurred up to six days after the last dose of study medication was administered.

8.1.7.3.2 Analyses focused on Outliers

Appendix 8.7.3.2 includes the sponsor's criterion of clinically significant changes as well as the incidence of these events in the placebo-controlled studies. It can be inferred from this table that statistical significance using the Fisher exact two-tailed test was seen for weight increase only. Again, it must be considered that the baseline values may have been compared to a vital sign measurement that was taken up to six days after the last day of study treatment.

8.1.7.3.3 Dropouts for Vital Sign Abnormalities

The table below presents the number of subjects who withdrew because of vital sign abnormalities in the original NDA submission database. A similar table was not submitted in the sponsor's safety update data.

Subject withdraws for abnormal vital signs or weight measurements in Phase II/III trials (adapted from sponsor's electronic submission)

	Ziprasidone	Haloperidol	Risperidone	Placebo
Number of Subjects Randomized:	2140	407	206	364
HYPERTENSION	4 (0.2)	0	1 (0.5)	0
HYPOTENSION	1 (0.0)	0	0	0
POSTURAL HYPOTENSION	1 (0.0)	0	0	0
TACHYCARDIA	4 (0.2)	1 (0.2)	0	0
WEIGHT GAIN	1 (0.0)	0	0	0
WEIGHT LOSS	3 (0.1)	0	0	0

The following table itemizes the case reports of subjects who discontinued because of vital sign abnormalities. There is some discrepancy for the number of subjects who discontinued because of weight changes, because there were only two case listed in the sponsor's line listing of subjects for this item; however there were two cases of weight loss listed as serious adverse events (please refer to Appendix 8.1.2 under metabolic).

Subjects who discontinued due to vital sign abnormalities

Subject ID #	Age/Sex	Modal Dose /duration	Reason for d/c	Outcome/comments
116B-0617001	26/F	160 mg 139 days	weight gain	Subject reported weight gain. Investigator did not record weights.
116B-0572000f	37/M	200 mg 127 days	weight loss	Subject's weight fluctuated (baseline: 123 lb.; at discharge: 118.5; overall loss: 4.5 lb.). There was 10 lb. weight gain in first 6 weeks and then 14.5 lb. weight loss within the next two month before d/c.
117-6840608	43/M	80 mg 7 days	hypertension	Termination sitting blood pressure was 160/120 with heart rate 124 bpm. Baseline values: 145/100; 84bpm. No orthostasis.
303-2120222	58/M	160 mg 349 days	hypertension	Syncopal episode: loss of consciousness for 2-3 minutes. Upon recovery, blood pressure was 180/90 with 130 bpm. No significant ECG change. Returned to baseline the next day. CT-scan showed cerebral neoplasm with edema I temporo-parietal region of right hemisphere.
104-5220146	45/F	80 mg 12 days	hypertension	Subject had history of hypertension and diabetes with concurrent medications of nifedipine and glyburide. She awoke in the middle of the night feeling weak and tremulous and had a blood pressure of 195/105. Ziprasidone was d/c and nifedipine was increased. Over the next three days blood pressure fluctuated from 170/90 to 142/84
106-5520124	41/M	40 mg 15 days	hypertension	Blood pressure: baseline: 100/70 (sitting) at d/c: 148/112 (sitting)
Subjects who discontinued due to vital sign abnormalities (con't)				
Subject ID #	Age/Sex	Modal Dose /duration	Reason for d/c	Outcome/comments
303-1970265	68/M	40 mg 7 days	hypotension	Subject was hypotensive at baseline.
106-5420149	31/M	120 mg 14 days	tachycardia	Pulse at baseline: 122 bpm at d/c: 138 bpm
117-7060380	30/M	80 mg 12 days	tachycardia	Recorded as severe tachycardia, but heart rate not available in patient profile or case report.
115-6470383	40/M	80 mg 3 days	tachycardia	Baseline: ECG: possible lateral/inferior infarct with pulse: 74 bpm, but cardiologist determined this was not an infarct. QTc:408.7 At discharge: pulse: 119 bpm, QTc:445.0

8.1.7.4 Additional Analyses and Explorations

There were no additional studies or analyses of vital signs done by the sponsor.

8.1.8 ECGs

8.1.8.1 Extent of ECG testing in the development program

ECGs were recorded in all Phase II/III trials. The tracings were read on site for the short term placebo controlled and most other studies. Study 303, the 52 week placebo controlled study, had ECG tracing initially read on site and then they were sent to Premier Research Worldwide of Cambridge England for blinded reading. In the original NDA submission, the ECG results of study 303 were kept separate as a different data set within the NDA data base. However, a resubmission of the data (11/13/97) included an analysis and consult by Joel Morganroth, M.D. in which the data sets from study 303 were integrated into the entire data base of the NDA, and ECGs suspected of being read by an automated system were reread by a more accurate system of analysis (Please refer to Section 8.1.8.4 for details). The tables of data submitted in Dr. Morganroth's reanalysis (submission of 11/13/97) will be used for the purposes of this review.

As part of the review process, Charles J. Ganley, M.D., cardiology consultant at FDA (review of 11/18/97) stated that ECGs were performed at trough times in some studies and the timing in other studies was unclear. He also addressed concerns regarding the dose dependent response for QT and QTc prolongation observed in some studies within this submission (11/18/97 & 1/6/98).

8.1.8.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

As done in the review of clinical laboratory and vital sign analyses, the main focus of this section of the review will be on pooled ECG data from the short term placebo controlled studies: 104, 106, 114, 115. This allows for comparison to be made to the placebo group and may eliminate any confounding variable of time period since the duration of treatment between the groups in these studies is comparable. Within this pool of data, there were 656 ziprasidone subjects and 250 placebo subjects for comparison. The tables used will reflect the most recent data reanalysis submitted by the sponsor (11/13/97).

8.1.8.3 Standard Analyses and Explorations of ECG Data

8.1.8.3.1 Analyses Focused on Measures of Central Tendency

Appendix 8.1.8.3.1 presents the mean change from baseline to the most abnormal value of ECGs from the short term placebo controlled studies. It is important to compare baseline to the most abnormal value, because the last observed value was collected up to six days after the last dose which may reflect less drug effect due to the half life. The sponsor did not provide a statistical analysis comparing placebo with the treatment groups with this reanalyzed data. From observation, it appears that subjects in the ziprasidone groups manifest more frequent ECG changes of QTc increase and heart rate than is seen in the placebo and haloperidol group. Below is a table summarizing these two parameters.

Summary of maximum mean changes in ECG of Short term placebo control studies

	Ziprasidone Daily Dose (mg/day)					Placebo	Haloperidol
	<80 (n=230)	80 (n=138)	120 (n=111)	160 (n=100)	≥200 (n=77)	(n=250)	(n=76)
QTc	8.6	12.6	15.2	19.8	15.0	4.3	4.1
Heart rate	7.8	6.6	5.4	6.7	4.4	4.5	4.4

As observed by Dr. Ganley's review (11/18/97 & 1/6/98), it can be seen that there is a dose response for the mean QTc change for doses less than 200 mg of ziprasidone.

8.1.8.3.2 Analyses focused on Outliers

Appendix 8.1.8.3.2 presents the sponsor's reanalysis of the incidence by percent of QTc changes collected from ECGs in the short term placebo controlled studies. The sponsor only submitted data on the incidences of QTc changes and did not submit information regarding the incidence of change in other ECG parameters.

In the original submission, the sponsor included a consult from His observation based on the original data base was that the most frequent ECG changes were from normal ST-T to abnormal ST-T with instances of isolated prolongation of the P-R, QRS, appearance of LVH, LAFB and rare PVC; Dr. Fisch did not feel that these finding were significant and he did not observe them to be dose related.

8.1.8.3.3 Dropouts for ECG Abnormalities

The sponsor did not provide information specifically itemizing subjects who withdrew because of ECG changes. The following table of subjects who discontinued due to ECG abnormalities was generated from the pool of all oral dosing phase II/III subjects.

ECG-Related Withdrawals

SUBJECT #	AGE/ SEX	DOSE (MG/D)	LENGTH OF TREATMENT	SERIOUS ADVERSE EVENT/ COMMENTS
116B-6360004	69/F	80	approx. 8 months	Arrhythmia; Holter monitor showed frequent ventricular ectopy with ventricular couplets and bigeminy and supraventricular ectopy.
106-5420149	31/M	120	14 days	sinus tachycardia (138 bpm)
109-5650041	51/M	80	3 days	tachycardia-discussed as Possible NMS (See section 8.1.2.1)
117-7060380	30/M	80	12 days	sinus tachycardia (from CRF: 132 bpm) QT: minimal change from baseline
115-6470383	40/M	80-200	3 days	sinus tachycardia (119 bpm) QTc:screening:396 baseline: 408.7 termination 445.0 post study:423.8 post study: 396.2

8.1.8.4 Additional Analyses and Explorations

The sponsor's submission dated 11/13/97 included a copy of a cardiology consult prepared by Within this submission, reported his additional analysis of the ECG data from the integrated safety data base; this included a blinded rereading of 3,883 ECGs using a central laboratory for purportedly more accurate QTc duration measurement to correct inaccuracies caused by automated readings of the ECG data. Using this method, concluded that of the 34 subjects originally identified as demonstrating QTc interval of ≥ 500 or having an increase of ≥ 75 msec, only one subject (116B-6220003) actually fulfilled the criteria of a QTc interval increase of ≥ 75 msec. No subjects were found to have a QTc measurement greater than 450 msec.

Dr. C. Ganley of HFD-110 also reviewed the ECG data in the integrated safety data base. Please refer to his reviews dates 11/18/97 & 1/6/98.

Because the sponsor allowed for the final ECGs to be recorded up to six days after the administration of the last dose, Dr. Boehm (HFD-120: 1/23/98) conducted an analysis that excluded any QTc value of subjects whose final ECG was recorded at one day or more after discontinuing ziprasidone in study 101 (the protocol required that the time of the ECGs be recorded); a comparison of baseline-to-final QTc was then recalculated. Dr. J. Boehm's results suggest that the mean baseline-to-final QTc changes recorded less than 1 day after discontinuing the drug were similar to the mean QTc measurements when the final ECG reading was taken up to 6 days after discontinuing the drug.

In the submission of 3/20/98, the sponsor expressed concern that the methodology of recording the initial QTc affects the determination of QTc prolongation. The sponsor explained that they recorded both screening and baseline values (with a wash out period in between) and claim that there was a dose dependent relationship of QTc prolongation observed with the baseline-to-final QTc measurements, but not with the screening-to-final. They expressed their concern that NDA data bases from recently approved anti-psychotic agents utilized measurements of screening value to determine if QTc prolongation was present. It is important to note that according to eport (sponsor's submission of 11/13/97), there was a dose dependent QTc prolongation observed in both screening-to-maximum QTc value and the baseline-to-maximum value in ziprasidone treatment groups (although, the screening-to-maximum is of a lower magnitude).

Both Dr. Ganley and , report present data suggesting a dose dependent increase in QTc for doses up to and including 160 mg daily of ziprasidone in the short term placebo controlled studies. Both reports also discuss that a QTc increase is not demonstrated in the analysis of the 52 week study 303.

Based on the evidence that ziprasidone has been shown to cause an increase in the QTc interval as a function of dose within the proposed therapeutic range (80-160 mg daily), Dr. Ganley concludes that the risks of arrhythmia, syncope, and sudden death may exist for ziprasidone, because these risks have been observed with other drugs which also prolong the QTc interval. He stated also that the labeling should clearly reflect this risk and that it may be necessary to consider this drug as a second line therapy if approved.

8.1.9 Special Studies

8.1.9.1 Ophthalmology

The sponsor did ophthalmology examinations including slit lamp exam in some of the long term studies (Studies 104E, 106E, 108, 108E, 109E, 116B, 117, 303). The sponsor provided the following superficial analysis of this data in the ISS:

Ophthalmology Data: Incidence of Significant Changes from Baseline
All Evaluable Oral Dosing Phase II/III Studies

Number of Subjects	Ziprasidone 1168				Haloperidol 104				Risperidone 147				Placebo 84			
Changes From Baseline	Yes		No		Yes		No		Yes		No		Yes		No	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	43	(8.0)	491	(91.9)	3	(6.0)	47	(94.0)	3	(5.4)	52	(94.6)	4	(6.1)	61	(93.8)

* Visit day relative to start of open label treatment.
Protocols: 104E,106E,108,108E,109E,116B,117,303

A review of the incidence of all adverse events in the original integrated safety data base (not including the update) revealed that there were no prominent patterns of eye dysfunction that would merit a more detailed analysis at this time. Of note, there was one subject reported with cataract and 87 subjects (4% of 2140 subjects) who reported abnormal vision, not otherwise specified.

8.1.9.2 Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS) were assessed through the use of the Simpson Angus Rating Scale (SARS) and the amount of use of benztropine in subjects participating in studies 114 and 115, two of the pivotal six week placebo controlled studies. The following were the results observed:

1. When considering only subjects not treated with benztropine in study 114, a higher percentage of subjects in the 80 mg bid dose group had SARS scores (indicating more symptomatology) than in the 40 mg bid dose group. Both ziprasidone treatment groups had consistently higher scores than placebo. (see Appendix 8.1.9.2a). In study 114, twice as many subjects in the ziprasidone groups (40 and 80 mg bid) required the use of benztropine than in the placebo group (see Section 7.2.2 for details).

2. Results of study 115 showed a higher percentage of subjects with an increased SARS score in all ziprasidone groups compared to placebo. In study 115, benztropine was required in the 100 mg bid group approximately 1.5 times more often than in placebo group subjects; the 20 and 60 mg bid ziprasidone group's use was comparable to placebo use (see Section 7.2.3 for details).

Akathisia, a symptom of EPS, was measured using the Barnes Akathisia Scale (BAS) in both studies 114 and 115; propranolol was the medication identified to treat akathisia in the study 114 protocol and was listed as the concomitant medication to be used for EPS in study 115. The following were the results observed:

1) In study 114, the percentage of subjects who had an increase in the BAS (including only subjects who had not taken beta-blockers) showed higher scores (indicating more symptomatology) in both ziprasidone treatment groups compared to the placebo group at the last visit (see Appendix 8.1.9.2b). In study 114, beta blocker use in the ziprasidone treatment groups increased with higher dosing and was utilized more frequently than in the placebo group (see section 7.2.2).

2) In study 115, fewer subjects in the ziprasidone treatment group had an increase in BAS scores in the compared to placebo (see Appendix 8.1.9.2b), while blocker use in the ziprasidone groups was similar in slightly lower than in the placebo group (see section 7.2.3).

In conclusion, results from study 114 reveal that subjects in the ziprasidone groups consistently experienced EPS and akathisia more than subjects in the placebo group. Results from study 115 show a higher experience of EPS in ziprasidone groups versus placebo, but not akathisia.

8.1.10 Withdrawal Phenomena/Abuse Potential

The sponsor did not study the abuse potential nor the effects of sudden or gradual discontinuation of ziprasidone treatment. There were no reported case of withdrawal reaction.

8.1.11 Human Reproduction Data

The sponsor did not address this topic in the ISS and a request for information was required. The following table summarizes the subjects known to become pregnant while taking ziprasidone .

Subject #	age	ziprasidone exposure	Outcome and comments
304(E)-00390345	33	Subject had taking ziprasidone 80 mg for eight months; undetermined when pregnancy occurred.	Uterine bleeding: 1day after stopping ziprasidone Spontaneous abortion:2 days after stopping ziprasidone.
115-07350541	26	1st trimester (single 40 mg dose)	Term Infant with Tetrology of Fallot
116B-0523003*	31	1st trimester (160 mg x 8 days)	Abortion; no medical complications reported
301-02730246	28	1st trimester (20 mg x 7 days)	Healthy baby girl

This represents a limited number of exposures during pregnancy; therefore, no definitive conclusions can be drawn from this data.

8.1.12 Overdose Experience

The sponsor reports in the Integrated Summary of Safety that there were three subjects taking ziprasidone who experienced an overdose; the sponsor does not offer a specific definition of overdose. It is possible that one subject (116B6220002) experienced the sequela of ataxia; otherwise, there is no apparent sequela in the subjects who overdosed with ziprasidone. The following table summarizes the overdose cases:

Subjects with overdose of ziprasidone

SUBJECT #	AGE/ SEX	OVERDOSE MG	CONCOMITANT MEDICATIONS	COMMENTS
116B5870007	22/M	640 mg	lorazepam	Hospitalized for nausea, vomiting, shakiness, sweats, headache. Event resolved 4 days later, but treatment not recorded in submission.
116B6220002	28/M	480 mg	lorazepam, ranitidine, aluminum hydroxide/ magnesium hydroxide	Leukocytosis (also observed one month prior to overdose), slowed speech and unsteady gait. Subject was hospitalized for observation and discharged 3 days later with ataxia. Follow-up information was not located in this submission.
116B5950022	29/M	1880 mg	lorazepam, acetaminophen , topical starch suppository	Reported to also take alcohol and paroxetine. No signs or symptoms present. ECG reported to be normal. Gastric lavage revealed no pills.

Subject who was over accidentally overmedicated with ziprasidone

SUBJECT #	AGE	OVERDOSE MG	CONCOMITANT MEDICATIONS	COMMENTS
116B06820005	52/M	200 mg qd x 2 weeks	lorazepam, benztropine, chloral hydrate	Dosage was supposed to be 80 mg qd. Subject hospitalized for ↑ insomnia, restlessness, and Parkinsonism.

8.1.13 Pediatric Studies

There were two studies (044 and 122) described in the user fee extension submission (1/23/98) in which pediatric subjects diagnosed with Tourette's Syndrome were exposed to ziprasidone (note: there was no data submitted for a trial in pediatric subjects suffering with psychosis).

In study 044, an open label single dose (up to 20 mg ziprasidone of a liquid suspension) pharmacokinetic study in 15 children ages 7-16 y.o. with Tourette's Syndrome, adverse events were: 1) a 15 year old with a

syncopal event 3 hours and 41 minutes after a single oral dose of 20 mg (which corresponds to the $t_{½}$ range of 3.3-4.7 hours determined in this study), 2) postural hypotension observed in 2 subjects, 3) somnolence seen in 10 of the 15 subjects, 4) an increase in prolactin levels observed in all subjects with a peak elevation at 2-4 hours post dosing , and 5) other events including nervousness, dizziness, nausea and abdominal pain. Of note, one subject (07440011) demonstrated pharmacokinetic data that reflected an exposure of up to 10 times greater than the exposure of subjects from the same treatment group of 10 mg ziprasidone; this subjects data was not incorporated into the preliminary report's calculations of mean pharmacokinetic data.

In study 122, a double blind, placebo controlled, 8 week flexible dose (maximum: 20 mg bid ziprasidone) trial, 16 pediatric subject (ages 7-16) with Tourette's Syndrome were exposed to ziprasidone. All of the subjects treated with ziprasidone experienced adverse events during the study; the most commonly reported was somnolence (12 of 16 subjects). Of note, one subject (07440020) developed a new onset of abnormal involuntary tongue movements (suggestive of a dyskinesia) on day 59 of ziprasidone treatment which continued until day 80 when he was treated with risperidone and buspirone and was discontinued from the study. Another subject (07430014) a 15 y.o. male developed gynecomastia . Other adverse events included: akathisia, insomnia, depression, dizziness, headache, arthralgia, urinary incontinence, and dysuria.

8.2 Adequacy of Patient Exposure and Safety Assessments

8.2.1 Adequacy of Clinical Experience

The clinical data of this NDA appears to be based on an adequate subject exposure of the adult population. The duration of exposure and the total number of subjects is comparable to other recently submitted NDAs for the indication of psychosis. The sponsor submitted more than one adequate and well controlled study to support the efficacy claims of ziprasidone.

Data from two pediatric studies (Studies 044 and 050) exposing ziprasidone to children with Tourette's Syndrome were included as part of the major amendment to the NDA which extended the User Fee Date by 3 months. The material submitted for this new molecular entity entailed an exposure of ziprasidone in 15 children with a single dose and 18 children exposed to ziprasidone for less than 60 days. Also, this amendment did not include any studies in children diagnosed with psychotic disorders, the indication for which this NDA has been submitted. Therefore, the pediatric data submitted thus far is not adequate to provide appropriate safety labeling for children and adolescents at this time.

8.2.2 Adequacy of Animal and/or In Vitro Testing

With respect to QTc prolongation, the preclinical cardiovascular testing in the original NDA submission did not include in vitro studies to assess ziprasidone's effect on potassium channels or on duration of action potential in Purkinje fibers. The sponsor was requested in a letter on October 3, 1997 to conduct these in vitro studies and to characterize the action potential duration in Purkinje fibers for ziprasidone , the major metabolites of ziprasidone and an active comparison group such as sotalol or terfenadine. The request suggested using multiple concentrations of each agent to generate dose response curves.

In a meeting package (2/13/98), the sponsor concluded that ziprasidone and the metabolite ziprasidone-sulfoxide did not demonstrate significant effects on the action potentials of Purkinje fibers in dogs; FDA cardiology consultants (HFD-110) expressed concern that the sponsor did not test a high enough concentration of ziprasidone in this study to fully characterize the effects of ziprasidone in the therapeutic dosage range (note: the sponsor has not submitted a study report for review). In a meeting with FDA and the sponsor (3/27/98), the sponsor presented a brief summary of data which suggested that ziprasidone may inhibit the I_{kr} channel, an ion channel implicated in the process of QTc prolongation (no data was submitted for review).

8.2.3 Adequacy of Routine Clinical Testing

This submission was of adequate quality to be submitted for review. There were some concerns of what categories the sponsor chose for some serious adverse events; this is discussed in detail in section 8.1.2.1. Originally the sponsor submitted the data with the inclusion of clinical trials conducted by Drs.

..., it was requested that the sponsor re-evaluate the data excluding data from these sites. The sponsor concluded that the safety profile from Dr. site was consistent with the overall NDA data base. They also reported that the efficacy data was not significantly affected by the exclusion of Dr. data.

Most of the ECG recordings obtained in this data base were performed without regard for timing. There was no study which observed ECG recordings/QTc measurements at times of peak concentrations of ziprasidone. Also of concern is that no subject in these studies wore a Holter monitor. There is a possibility that QTc changes may have been more pronounced or perhaps evidence to the contrary could have been collected if ECGs had been collected just after peak doses were administered. A Holter monitor might have also provided insight into the multiple episodes of syncope observed if those patients had been monitored.

There were also a methodological flaw in the collection of the vital signs. Most of the vital signs recorded were done with sitting blood pressure rather than blood pressure recorded in the supine position; this does not allow for the most accurate assessment of orthostatic effects of ziprasidone. Also, in looking at the median changes from baseline of vital signs, the sponsor used observations that could have been recorded up to six days after the last day of study treatment; this may provide less accurate comparisons than could have been made if these measurements were recorded sooner given the half-life of this drug ($t_{1/2}$ =6.6 hours).

The elaborate system used by the sponsor for reporting clinical significance of laboratory values set up many restrictions that may not have captured laboratory abnormalities of interest. The criteria for a change from baseline for a baseline-abnormal subject appears extreme, and changes that may be concerning would not be picked up using this system. It would perhaps be more helpful to identify changes from baseline and use that as the criteria. It is curious that there were a significant number of subjects who had an abnormal baseline to merit different criterion; however, their laboratory values were not so abnormal that they were excluded from enrolling in the study. Also of note is that the last laboratory value was performed up to 6 days after the end of the study; some subjects may no longer have had appreciable plasma concentrations when the tests were performed, and the maximum effect of ziprasidone may not have been appreciated.

In the placebo controlled studies, there were only two subjects evaluated for prolactin studies; no thyroid studies were conducted in the placebo controlled studies. It would have provided more accurate information to assess these changes with placebo control studies; instead inference had to be made from a pool of data that included studies of different designs and duration.

8.2.4 Adequacy of Metabolic Workup

The sponsor conducted phase I studies in healthy adults testing the concomitant use of ziprasidone and carbamazepine, cimetidine, or Maalox ® in healthy adults. However, conclusions regarding concomitant use of carbamazepine was based on results from a study which used a dose which was lower than the recommended dosage range (please refer to Section 6.0 for detail). It would be most useful for the sponsor to test concomitant use of therapeutic doses of carbamazepine to make a more accurate conclusion of its effect.

8.2.5 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by New Drug; Recommendations for Further Study

For reasons discussed above, it would be helpful to assess ECG monitoring more closely with a Holter monitor to assess QTc changes during concentration peaks. One suggestion is to challenge subjects with higher doses to prove or disprove the existence of a dose effect changes of the QTc.

To further investigate the sponsor's claim that the QTc was not adequately tested in recently approved antipsychotic medications, it would be helpful to have a study characterizing the QTc of ziprasidone and other marketed drugs in which all ECGs were evaluated at a baseline after a wash out period. If all subjects in such a study were using a Holter monitor, it might provide clarity regarding each of these drugs effect on the QTc interval.

8.2.6 · Assessment of Quality and Completeness of Data

No electronic data sets were made available as part of the electronic submission, and all data was assessed from the grouping done by the sponsor's tables. Therefore, the laboratory abnormalities were determined by the sponsor's fixed criterion.

There were some items that did not offer consistency in the NDA. As an example: the listing of cataracts in a summary analysis: in Table H.5.2a, there are no incidents of cataract reported in all phase I/II/III studies. However, in Table H.5.8a there is one listing for cataract in this pool of all phase II/III studies. The ISS gave only a cursory summary of rashes experienced in this data base, and more detail would be necessary to help characterize this adverse event.

Another example of inconsistency was the reporting of syncopal episodes. There were 3 subjects experiencing syncope found by review of the patient narratives (108-6050002, 108E-5550096, 108E-5780052) who were not listed in the sponsor's listing of subjects with adverse events (Appendix VI table 1b of sponsor's submission of 3/18/97). This leaves some question as to whether all syncopal episodes were considered when the calculation the total of subjects with syncope listed in their calculations of incidence (Table H.5.8a of sponsor's submission 3/18/97).

Given that there is so much concern for the effects of ziprasidone on QTc measurements, it would be most helpful for the sponsor to analyze and submit results of all ECGs that have been performed when a subject has been taking ziprasidone whether they have been obtained by scheduled or unscheduled visits. It would also be helpful to have subjects on Holter monitors especially if they are subjects who have already shown that they have ECG changes or symptoms such as syncope associated with the use of ziprasidone.

8.3 Summary of Selected Drug-Related Adverse Events

8.3.1 Sudden Death

The sudden unexpected death rate for the ziprasidone safety update is 9.1 SUD per 1000 subject years (7/2565) [note: the cut-off date for the deaths was 5/15/97; the sponsor did not respond to requests to specify the cut-off date for calculating the subject years (i.e. the denominator)] (see section 8.1.1, p.28).

There are a variety of classification schemes to determine sudden unexpected deaths. However, under the scrutiny of different classification schemes, ziprasidone's rate of SUD rate continues to present a signal of risk. As discussed in Section 8.1.1 (p.28), using the scheme of classification by Dr. J Boehm (HFD-120: 2/3/98), ziprasidone was found to have a SUD rate that was 6 times higher than the SUD rate from a pool of combined data of recently approved antipsychotic NDAs. The SUD rate calculated in section 8.1.1 (p.27) of this review utilized a less inclusive classification, and resulted in a similar SUD count as that provided by the sponsor (submission of 3/20/98: using 5/15/98 cut-off). Using this less inclusive SUD

count, ziprasidone continues to surpass the SUD rate of the recently approved antipsychotics olanzapine, risperidone, and quetiapine. The SUD rate of ziprasidone is comparable to sertindole, an antipsychotic NDA withdrawn by the sponsor because of safety concerns regarding QTc prolongation, high sudden death rates in clinical trials and post marketing data from the U.K. showing a high SUD reporting rate (see section 2.2, p. 2). Since ziprasidone is not currently marketed in any country, the SUD rate of ziprasidone used in the less monitored and less restricted environment of a marketed drug is not available at this time.

8.3.2 QTc prolongation

Clinically, Ziprasidone has been shown to prolong the QTc interval in a pool of the short term placebo controlled studies (see section 8.1.8.3.1, p. 45) compared to both placebo and haloperidol in a dose dependent manner. It must also be mentioned that there was no regard for the timing of the ECG in those studies and the effect of ziprasidone on the QTc at peak concentration of ziprasidone remains unknown. The sponsor expressed concern that NDA data bases from recently approved anti-psychotic agents utilized a different methodology to ascertain QTc prolongation--using screening ECGs rather than baseline readings which are recorded after a wash out period (see section 8.1.8.4, p. 46). However, when either screening or baseline QTc values are compared to the maximum QTc, ziprasidone increases the QTc values in a dose related fashion (although, the screening-to-maximum is of a lower magnitude).

Drug induced QTc prolongation may be correlated with the development of ventricular arrhythmia, syncope, and sudden death (Morganroth, 1993). Though the ziprasidone safety data base is limited, there is already a signal of a higher SUD rate when compared to other recently approved antipsychotic NDAs. No subject--not even subjects who experienced syncope--underwent Holter monitoring. Holter monitoring may have provided insight into the multiple episodes of syncope observed in this data base (see section 8.2.3 p.51).

Based on the evidence that ziprasidone has been shown to cause an increase in the QTc interval as a function of dose within the proposed therapeutic range (80-160 mg daily), Dr. C. Ganley, FDA cardiology consultant (HFD-110) concluded that there may be the usual risks observed with drugs which prolong the QT interval. He stated also that the labeling should clearly reflect this risk and that it may be necessary to consider this drug as a second line therapy if approved.

8.3.3 Hypotension/Syncope

Because ziprasidone demonstrates alpha adrenergic properties, it is not unexpected that orthostatic hypotension and syncope were observed as adverse events in this data base (see section 8.1.2.1, p. 29). It should be noted that most of the vital signs recorded in this data base were done with sitting blood pressure rather than blood pressure recorded in the supine position; therefore, orthostatic changes may not be completely appreciated (see section 8.2.3, p.51). Despite this methodological flaw, postural hypotension was seen to have a statistically significant dose response relationship (see section 8.1.5.5, p. 39).

Syncope was reported to occur in 0.7% (15/2140) of subjects in the phase II/III safety data base (cutoff 10/31/96), while hypotension (combining postural hypotension and hypotension) occurred in 2.5 % (53/2140) of subjects in the phase II/III safety data base (as per sponsor's submission of 3/18/97: Table H.5.8). Postural hypotension occurred at a higher frequency in ziprasidone groups (1.3%) compared to placebo (0.4%) in the short term placebo controlled studies (Appendix 8.1.5.3).

There were 5 syncopal events and one hypotensive event considered to be serious adverse events (see section 8.1.2.1: p.29 and section 8.1.5.2 p. 37); however, it is unclear what criteria the sponsor used to report a syncopal event as a serious event . There were at least thirteen episodes of syncope in the Phase II/III data base that were not reported by the sponsor as a serious adverse event (see section 8.1.2.1: p.29). It is possible that the actual incidence of syncope may be higher than 0.7 % because of an inconsistency found in the presentation of the safety data base (see section 8.2.6 p. 52).

It is also noted that syncope is associated with other drugs which prolong the QTc interval. Unfortunately, subjects who experienced syncope were not monitored more closely with a Holter to determine possible etiology of their syncopal events.

8.3.4 Rash

Rash was the most common adverse event resulting in withdrawal from the ziprasidone treatment groups (see 8.1.3.2, p.36). When viewing the sponsor's table of incidence of treatment emergent adverse events (submission 3/18/97: Table H.5.8a), events related to skin and appendages occurred in 10.2 % (218/2140) of subjects. The 1 % table states that rashes occurred in 4.1% (29/702) of ziprasidone subjects in the short term placebo controlled studies, compared to the placebo rate at 3.3% (see Appendix 8.1.5.3). There also was a dose response relationship seen with the occurrence of rashes (see section 8.1.5.5 p. 39).

There were 21 subjects who discontinued for rashes in the originally submitted integrated safety data base; the haloperidol group only had 2 withdrawals, while the placebo group had 1 withdrawal. It was left to the investigator's discretion as to whether or not an event was reported as serious, and there did not appear to be any consistent feature that merited reporting a rash as a serious event (see section 8.1.2.2, p.30).

It was necessary for this reviewer to go through the line listings of subjects with adverse events (sponsor's submission of 3/18/98: Appendix VI Table 1b) and then follow this up with relevant patient profiles in order to gain a better understanding of the rashes in this NDA data base. This review revealed that there were several subjects whose rash was accompanied by an elevated white blood count, and at least two subjects with rash whose eosinophil count was elevated. Most cases of rash resolved within one week of discontinuing ziprasidone; one subject experienced "bullous drug eruptions/ pruritic blisters with post-excoriated papules" on the hands, wrist, scalp, and neck which resolved 24 days after discontinuing ziprasidone. Medications used to treat rashes included steriods (oral and topical) and antihistamines. Three subjects required prolonged hospitalization to observe their rashes. (See section 8.1.2.2, p.31)

Since the sponsor's summary of the rashes in the ISS was found to be inadequate, it is recommended that the sponsor compile a detailed and thorough summary of the description, duration, related hospitalizations, severity, accompanying symptoms, treatment and resolution history of all cases of rashes observed in this NDA safety data base.

8.3.5 Seizure

In the safety update (submitted 8/29/97), the sponsor reported that 1.8 subjects per 100 subject years (12/772) or 0.54 % (12/2588) of the subjects in the NDA data base experienced a seizure while taking ziprasidone. The original NDA submission (3/18/97) includes six subjects who discontinued as a result of their seizure or possible seizure activity. The safety update did not include specific subject information (see section 8.1.2.7, p. 34). If using ziprasidone, caution would be required for patients with a history of seizure disorder.

8.3.6 Cholesterol/triglyceride elevation

In the short term placebo controlled trials, the ziprasidone groups were shown to have statistically significant increases in both cholesterol and triglyceride when compared to placebo with respect to numbers of patients exceeding threshold values. Cholesterol levels were observed in 2 % (16/685) whereas placebo had 0%. Triglycerides increased in 12 % (85/684) of the ziprasidone subjects in these trials compared to an increase in 7 % observed in the placebo group (see section 8.1.6.3.2, p. 40 and Appendix 8.1.6.3.2c). The increase in cholesterol and triglyceride levels is not listed in the sponsor's 1 % table (Appendix 8.1.5.3) which should be corrected. Increased cholesterol and triglyceride levels may be considered risks for the development of atherosclerosis.

8.3.7 Hyperprolactinemia

Prolactin studies were monitored in only two subjects in the short-term placebo controlled studies, one of which was found to have abnormal values. Therefore, it is necessary to look at the total pool of oral dosing phase II/III studies; clinically significant abnormalities were identified in 20% (148/741) of ziprasidone subjects whose prolactin levels were monitored (see section 8.1.6.4, p. 42 and Appendix 8.1.6.4).

Amongst the sponsor's literature review were two studies (Bench, 1996; Bench, 1993) which reported large elevations of prolactin levels when comparing baseline and peak plasma levels of ziprasidone in twelve normal volunteers taking between 5 and 60 mg of a single dose of ziprasidone (see section 5.2.3 p.6).

An increase in prolactin levels was observed in all subjects with a peak elevation at 2-4 hours post dosing in a single dose pediatric study of 15 children ages 7-16 y.o (Study 044). Gynecomastia was observed in one 15 y.o. male with Tourette's Syndrome in Study 122. (see section 8.1.13, p. 49)

As many neuroleptics are associated with hyperprolactinemia, it is not surprising to observe this effect with use of ziprasidone.

8.3.8 Transaminases elevation

An elevated SGOT (AST) levels were observed in 0.3 % (6/1780) of subjects in the phase II/III study data base. Elevated levels of SGPT (ALT), a more specific enzyme indicative of hepatic cell activity, was observed in 2% (17/1776) of the subject in the phase II/III data base (sponsor's submission 3/18/97: Table H.5.18a.2).

Section 8.1.6.3.3 (p.41) provides a listing of subjects who dropped out because of abnormal liver enzymes; there were several subjects whose liver function studies elevated while taking ziprasidone and normalized one to twenty days after discontinuing ziprasidone, suggesting a positive dechallenge and drug relatedness. There were two subjects in this listing who were noted to have jaundice accompanying elevated LFTs; there was inadequate follow up reported for subject 301-2790615 (safety update) which would be required for complete assessment. Cases which the sponsor considered to manifest serious adverse event of elevated transaminase is found in section 8.1.2.4 (p.32). It is unclear how the sponsor determined whether or not a laboratory value was considered a serious adverse event.

Also of note is the case of a 49 y.o. female (subject 307-2690047) who eventually died of hepatic coma, cholestatic jaundice and malignant neoplasm 95 days after stopping ziprasidone. Her initial symptoms of jaundice and elevated AST (244 U/L) and ALT (375 U/L) first appeared after 196 days of taking a daily dose of 100 mg ziprasidone. It may be possible that the ziprasidone aggravated her already compromised liver.

8.3.9 Weight Gain

Weight gain of ≥7 % was observed in 10 % (61/622) of subjects taking ziprasidone in the short term placebo controlled phase II/III studies (see section 8.1.7.3.1, p. 43). There was a statistically significant increase in weight gain found in subjects taking ziprasidone compared to placebo. It is noted that weight gain in not recorded in the sponsor's 1 % table (Appendix 8.1.5.3) and fits the criteria to be considered a common and drug-related adverse event (see 8.1.5.4, p.39).

8.3.10 Extrapyramidal Symptoms (EPS)

EPS was observed often enough in the ziprasidone safety data base to be considered a common and drug-related adverse event (see 8.1.5.4, p.39). Its incidence was found to be 5 % (33/702) of the ziprasidone subjects in the short term placebo controlled phase II/III studies . As can be seen in the 1 % table, associated symptoms of akathisia, dystonia, and hypertonia were observed at higher rates in the ziprasidone-group compared to the placebo group (see Appendix 8.1.5.3).

EPS and akathisia, a symptom of EPS, were assessed in studies 114 and 115 using rating scales and use of concomitant medications (see section 8.1.9.2, p.48). It was found in studies 114 and 115 that subjects in the ziprasidone groups consistently experienced EPS to a greater magnitude than in the placebo groups. Study 114 results revealed that akathisia was experienced more often in the ziprasidone treatment groups, whereas study 115 did not support this conclusion.

A listing of subjects whose EPS was considered a serious adverse event can be found in Section 8.1.2.6 (p.33).

8.3.11 Neuroleptic Malignant Syndrome (NMS)

Although the ISS did not identify any cases of NMS, a review of the patient narratives revealed two subjects whose adverse event description could be categorized as NMS. These cases are also summarized in section 8.1.2.5 (p.31).

8.3.12 Somnolence

Somnolence was found to be a common and drug-related adverse event (see 8.1.5.4, p.39). It was also found to have a dose response relationship (see Section 8.1.5.5, p. 39). Somnolence was observed in 14.4% (101/702) of subjects in the ziprasidone group in the short term placebo controlled phase II/III studies (see Appendix 8.1.5.3)

8.3.13 Tardive Dyskinesia

Tardive Dyskinesia is associated with the use of most neuroleptics and the symptoms may be masked by the use of antipsychotics. It is difficult to determine ziprasidone's potential to cause tardive dyskinesia as most of the controlled safety data base is of short duration of exposure.

Of note, one subject (07440020) in pediatric study 122 developed a new onset of abnormal involuntary tongue movements (suggestive of a dyskinesia) on day 59 of ziprasidone treatment which continued until day 80 when he was treated with risperidone and buspirone and was discontinued from the study (see Section 8.1.13, p. 49). More information is needed from the sponsor to characterize this episode more clearly.

8.3.14 Aspiration Pneumonia

Aspiration pneumonia has been associated with neuroleptic use and should be considered as a possible adverse event. There were two cases of pneumonia seen in the ziprasidone safety data base (see section 8.1.2.6, p. 33). As a related symptom, cough was seen to increase in 2.6 % (18/702) of the ziprasidone subjects (compared to 0.7 % placebo subjects) in the short term placebo controlled phase II/III studies (see 1 % table: Appendix 8.1.5.3).

9.0 Labeling

If approved, the sponsor's labeling will need considerable revision. Please see section 8.3 for important concerns that need to be addressed in labeling.

10.0 Conclusions

In the wake of the uncertainty and disagreement in the cardiology community of the effects of a dose dependent QTc prolongation caused by a drug, it is difficult to determine whether this quality of ziprasidone presents a major health hazard. Clearly, more understanding and research (using consistent methodology) are needed to clarify this issue for ziprasidone as well as any antipsychotic which may have this potential. What is striking about ziprasidone is that an effect of QTc prolongation was observed in the short term placebo controlled studies irrespective of methodology (i.e. the QTc interval is prolonged when both screening-to-maximum and baseline-to-maximum measurements are made). Another relevant detail regarding ziprasidone's ability to prolong the QTc is that it has been found to be dose-dependent within the therapeutic dosing range in short term placebo controlled studies.

An important factor that must be considered in reviewing the safety of this drug is the sudden unexpected death (SUD) rate. It is concerning and alarming to view the ziprasidone safety data base against other recently reviewed antipsychotic NDA safety data bases. Even under different methods of SUD analysis, the rate of ziprasidone's SUDs clearly surpass similar drugs that have been recently approved.

In clinical practice, it is always important to weigh the balance of risks and benefits for each medication prescribed to a patient. There are currently 15 antipsychotic medications marketed in the USA, and physicians continue to struggle with finding adequate treatment for many schizophrenic patients who do not respond or cannot be treated by the available armamentarium of medications. It may be that ziprasidone would offer a unique treatment in individual cases. However, thus far, the sponsor has not shown that ziprasidone is of benefit to subjects who are refractory towards treatment with other available antipsychotic medications.

Although the sponsor may be claiming that the mean weight gain observed in the ziprasidone NDA safety data base reflects less of an increase than other marketed antipsychotics, ziprasidone is associated with weight gain. Weight gain of ≥ 7 % was observed in 10 % of subjects taking ziprasidone in the short term placebo controlled phase II/III studies, and this was shown to be statistically significant when compared to placebo.

Also, ziprasidone possesses the ability to induce extrapyramidal symptoms.

Ziprasidone has been shown to be effective in the treatment of schizophrenia in two placebo controlled studies. However, the risks appear numerous. Of most concern are the qualities it shares with sertindole, an antipsychotic NDA which was withdrawn by the sponsor because of safety concerns regarding QTc prolongation and high sudden death rates in clinical trials and post marketing data from the U.K. Since ziprasidone is not currently marketed in any country, we do not have the insight as to how this drug would affect a large population in an environment less monitored, less restricted and without a mechanism for informed consent.

11.0 Recommendations

According to Section 505 [355] of the Federal Food, Drug, and Cosmetic Act (July, 1993), approval of an application may be denied if the sponsor has not employed "adequate tests by all methods reasonably applicable" to show that the drug is "safe for use under the conditions prescribed, recommended or suggested in the proposed labeling," or if there is "insufficient information to determine whether such drug

is safe for use under such conditions." In the ziprasidone safety data base, there are still many uncertainties regarding the QTc prolongation, the etiologies of syncopal episodes (no Holter monitoring was used in the current safety data base), and the signal presented by the high sudden unexpected death rate.

Ziprasidone has been shown to be effective in schizophrenic patients yet it presents safety risks of unknown magnitude. Given that there are many antipsychotic drugs available whose NDA data base did not possess the qualities of both a high SUD rate and the ability to cause a dose dependent QTc prolongation, the risk benefit ratio does not support ziprasidone as a first line drug. To overcome the risk/benefit ratio, the sponsor would need to show that it can effectively treat patients who fail on other drugs. Even if approved as a second line drug, the risks of syncope, ventricular arrythmias, or sudden unexpected death need to be clearly stated in the labeling so as to alert physicians, thus enabling them to monitor patients appropriately. In light of the uncertainty of its safety profile and the unknown effectiveness in refractory patients, it is recommended that ziprasidone not be approved at this time.

/S/ 4/30/98

Roberta L. Glass, M.D.
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NDA 20-825
Div File
HFD-120:Laugren/Hardeman/Mosholder/Burkhart/Boehm/Glasss

5-8-98

While I am also concerned about the potential for cardiovascular risk associated with the use of ziprasidone, I do not believe this potential risk precludes entirely the possibility of approving this product. In my memo to the file, I have provided an alternative discussion of the data and issues pertinent to cardiovascular risk for ziprasidone, and I have provided a draft of labeling that I believe adequately describes the potential risks with ziprasidone and restricts its use in a way that makes it possible for it to be used in a reasonably safe manner for patients who fail on other products.

/S/ MD
Team Leader, DDP

LIST OF APPENDICES

Appendix 5.1.1.1 Summary of all trials (adapted from the sponsor's submission of 10/27/97; cut off date is 5/15/97)

	Ziprasidone		Haloperidol		Risperidone		Amisulpride	Other	Placebo	
Phase I Studies (Clinical Pharmacology)										
Single Dose Studies	409		4					38	71	
Multiple Dose Studies	333							11	78	
Subtotal: Phase I Studies	742		4					49	149	
Phase II/III Studies										
Oral Studies										
Placebo Controlled Studies										
Short-term Fixed-Dose Studies (1)	702								273	
Long-term Fixed-Dose Studies (2)	246	[27]							84	[9]
Short-term Flexible-Dose Studies (3)	16								12	
Long-term Flexible-Dose Studies (4)	17								10	
Active Controlled Studies										
Short-term Fixed-Dose Studies (5)	683		340							
Short-term Flexible-Dose Studies (6)	199		6		147		49			
Long-term Flexible-Dose Studies (7)	1252	[609]	267	[28]	156	[8]				
Uncontrolled Studies										
Short-term Studies (8)	86									
Long-term Studies (9)	6	[6]								
Subtotal: Oral Studies	2565*		585		295		49		370	
Dementia Patient Studies										
Short-term Flexible-Dose Studies (10)	11								12	
Single Dose Total	409		4					38	71	
Multiple Dose Total	2909		585		295		49	11	531	
Grand Total	3318		589		295		49	49	602	

Numbers in brackets represent the number of subjects included in the unbracketed number whose participation was in a continuation study under the same treatment as the parent study and are also counted in the parent study category for that treatment. These subjects are counted only once in totals and subtotals.
Protocol 115 subjects taking ziprasidone are counted in categories (1) and (4) but are counted only once in totals and subtotals.

(1) Includes studies 104, 106, 114, 115
(2) Includes studies 104E, 106E, 303
(3) Includes studies 122
(4) Includes studies 307
(5) Includes studies 101, 115, 301
(6) Includes studies 111, 302, 305
(7) Includes studies 116B, 117, 108, 108E, 304, 302E, 304E
(8) Includes studies 015, 102, 109, 110, 118
(9) Includes studies 109E
(10) Includes studies 105

*Does not include Studies 105 (n=11) and 120 (n=12)

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Appendix 5.1.1.2 **Table of all studies** (adapted from sponsor's submission of 10/24/97)

Pfizer Central Research Sponsored Phase I Clinical Pharmacology Studies	
128-001-US	Double-blind, placebo-controlled, parallel, single rising oral dose trial; healthy men (Ziprasidone: n=40, pbo: n=20); ziprasidone doses (0.5, 1,2.5,10,20,40,60,80,100 mg oral suspension).
128-002-US	Double-blind, pbo-controlled, multiple oral dose trial; healthy men (Ziprasidone: n=16, pbo n=5); ziprasidone dose range (20 mg qd to 40 mg bid) 16 days.
128-004-US	Open, randomized, 3-way crossover, single oral dose trial; healthy men (n=9); ziprasidone dose (suspension-fasting: 20 mg, capsule fasting: 2- mg; capsule-fed: 20mg).
128-005-US	Double-blind, pbo-controlled, multiple oral dose, parallel trial; healthy men (ziprasidone n=16, pbo: n=4): Ziprasidone dose range (20 mg qd to 80 mg bid). 18 days.
128-006-US	Open, non-randomized, 6-way crossover, single oral dose trial; healthy men (n=45): Ziprasidone dose (capsule-fed: 20mg: capsules-fasting: 40mg: capsules-fasting: 80mg: capsules-fed: 80 mg).
128-007-US	Open, three-way, crossover, oral single dose trial: healthy men (n=29): Ziprasidone dose (fasting: 20mg; fed: 20mg; 2 hr after meal: 20mg).
128-008-US	Open, non-randomized, crossover oral single dose trial comparative to Haloperidol: healthy men (n=5): Doses (Ziprasidone: 40mg; Haloperidol: 75 mg).
128-009-US	Double-blind, pbo-controlled, randomized, single oral dose, parallel trial comparative to Diazepam; healthy subjects (Ziprasidone: n=30, Diazepam: n=30: Pbo n=30): doses (Ziprasidone 20mg; Diazepam: 10mg).
128-010-US	Open, randomized, two-way crossover, single oral/IV dose: healthy men (Oral: n=12, IV: n=12); dose (capsules 20mg; IV: 5mg)
128-011-US	Open, randomized three-way crossover, oral single dose trial; healthy men (n=90): Ziprasidone dose (4x5 mg tablet; 1x20 mg tablet; 1x20 mg capsule).
128-013-US	Double-blind, pbo-controlled, multiple oral dose trial; healthy men (Ziprasidone n=29: pbo: n=10): Ziprasidone dose range (5 mg qd to 60 mg bid).
128-014-US	Open, randomized, two-way crossover, single oral dose trial, healthy men (n=12): Ziprasidone dose (2x20 mg capsule, 1x40 mg capsule).
128-015-US	Double-blind, pbo-controlled, multiple oral dose trial; subjects with schizophrenia or schizoaffective disorder (n=33): Ziprasidone dose (titrated to 160 mg/day), 24 days.
128-016-US	Open, randomized, six-way crossover single oral/IV/Nasoenteric infusion trial: Healthy men (n=28): Ziprasidone dose (20 mg).
128-017-US	Open, parallel, oral single dose, PET Scan study; healthy men (n=10): Ziprasidone dose (2x40mg capsule): PET Scan performed at 4,8, 12, and 18 hours post-dosing.
128-018-US	Open, randomized, two-way crossover, oral single dose, healthy men (n=12): Ziprasidone dose (3x20 mg capsules and 1x 60 mg capsule).
128-019-US	Open, randomized, two-way crossover oral single dose, healthy men (n=11): Ziprasidone dose (4x20 mg capsules and 1x80 mg capsule).
128-020-US	Open, non-randomized, single oral dose trial; healthy men (n=4): $^{14}C/^{3}H$-ziprasidone dose (20 mg oral suspension).
128-021-US	Open, randomized, two-way crossover, single oral dose fasting/fed trial: healthy men (n=12): Ziprasidone dose (40 mg tablet).
128-022-US	Open, randomized, two-way crossover, single oral dose fasting / fed trial; healthy men (n=12); ziprasidone dose (40 mg tablet).
128-023-US	Open, randomized, two-way crossover, single oral dose fasting / fed trial; healthy men (n=12); ziprasidone dose (40 mg tablet).
128-024-US	Open, randomized, two-way crossover, single oral dose fasting / fed trial; healthy men (n=12); ziprasidone dose (40 mg tablet).
128-025-US	Open, randomized, placebo-controlled, parallel, lithium interaction trial; healthy men (Ziprasidone + Lithium: n=12, pbo + Lithium: n=13); ziprasidone dose (2 x 20 mg capsules bid).
128-026-US	Open, parallel, multiple dose steady-state PK trial; healthy and renally impaired subjects (Group 1 CLcr >70: n=10, Group 2 CLcr 30-60: n=9, Group 3 CLcr 10-29: n=11, Group 4 hemodialysis: n=9); ziprasidone dose (20 mg capsules bid).
128-027-US	Open, non-randomized, single oral dose trial; healthy men (n=4); $^{14}C/^{3}H$-ziprasidone dose (20 mg oral suspension).
128-028-US	Open, parallel, multiple dose PK trial; healthy elderly (n=16) and young (n=19) subjects; ziprasidone dose (20 mg capsules bid).
128-029-US	Open, randomized, two-way crossover, single oral dose fasting / fed trial; healthy men (n=12); ziprasidone dose (40 mg oral suspension).
128-030-US	Open, parallel, multiple dose PK trial; healthy (n=14) and cirrhotic (n=16) subjects; ziprasidone dose (20 mg capsules bid).
128-031-US	Open, randomized, two-way crossover, single oral dose trial; healthy subjects (N=23); ziprasidone dose (capsules: 20 mg research vs. 20 mg commercial).
128-032-US	Open, non-randomized, cross-over, single intravenous escalating dose trial; subjects with schizophrenia or schizoaffective disorder (n=6); ziprasidone doses (2.5, 5, 10, 20, 40 mg).
128-033-UK	Investigator-blind, placebo-controlled, single escalating intramuscular dose trial; healthy males (Ziprasidone: n=16, pbo: n=5); ziprasidone doses (5, 10, 20 mg).
128-034-US	Open, randomized, two-way crossover, single oral dose trial; healthy subjects (n=12); ziprasidone doses (2 x 20 mg capsules vs 40 mg oral suspension).
128-035-US	Open, randomized, two-way crossover, multiple oral dose trial; healthy subjects (n=12); ziprasidone dose (20 mg research capsules bid vs. 20 mg commercial capsules bid).

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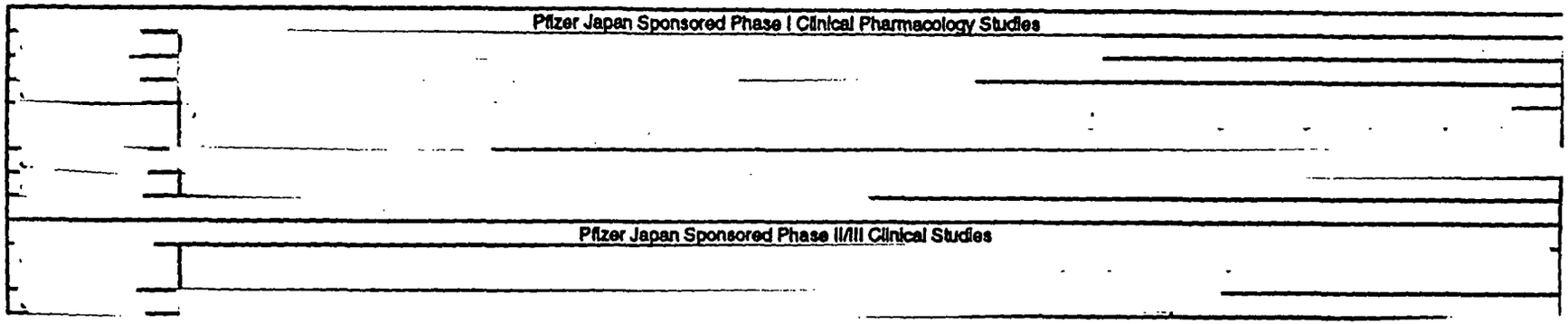
Ongoing Japanese Trials Contributing Safety Data in Original NDA Submission
(Japanese data reported separately and not incorporated into the NDA project database)



Additional Trials Reflected in Four-Month Safety Update
("n" reflects number of subjects in project database as of May 15, 1997 data cutoff)

	Pfizer Central Research Sponsored Phase I Clinical Pharmacology Studies
128-045-US	Open, randomized, three-way crossover, multiple dose trial; healthy subjects (n=13); ziprasidone doses (cross-linked capsules: 20 mg, uncross-linked capsules: 20mg).
128-050-US	Open, randomized, two-way crossover, multiple dose ketoconazole interaction trial; healthy subjects (n=14); ziprasidone dose (2 x 20mg capsules).
	Pfizer Central Research Sponsored Phase II/III Studies
128-307-EU	Fifty-two week, double-blind, randomized, flexible-dose, placebo-controlled trial; subjects with chronic or subchronic schizophrenia (Ziprasidone: n=17, pbo: n= 10); ziprasidone doses (40-60, or 80-100 mg qd).
128-308-EU	Open, flexible-dose, extension trial; subjects with non-organic psychosis (n=0); ziprasidone dose (20-100 mg bid).
	Pfizer Japan Sponsored Phase II/III Clinical Studies
JP-96-602	Fifty-two week, open, flexible-dose, extension trial (n=0); ziprasidone dose (20-60mg bid).

Trials Contributing Safety Data to Original NDA but not to Four-Month Safety Update
(Data from these trials are now contained in a separate intramuscular database)

128-120-South Africa	Five-day, open, non-randomized intramuscular to oral dose trial; subjects with psychosis (n=12); ziprasidone doses (intramuscular: 2.5 to 20 mg bid to qid, oral: 20 to 60 mg bid).
128-121-US	Open, randomized, haloperidol-controlled, multiple dose intramuscular and oral trial; subjects with psychotic disorder (n=0); ziprasidone doses (20 to 80 mg IM up to qid, 20 to 100 mg oral capsules bid).

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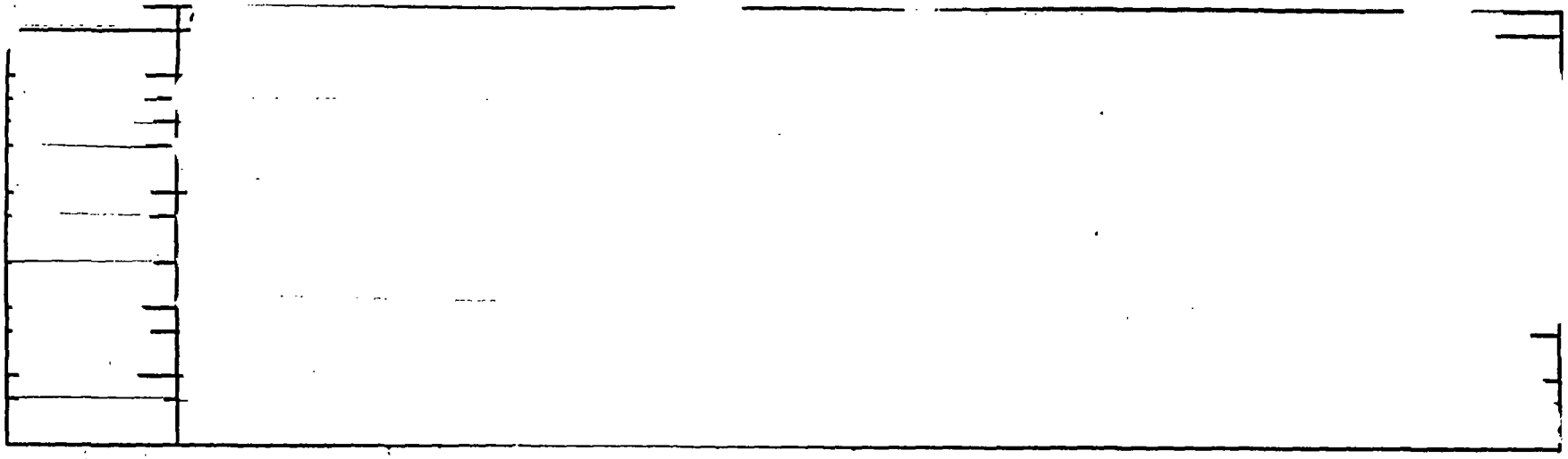

Pfizer Central Research Sponsored Phase II/III Studies	
128-101-US	Four-week, double-blind, randomized, parallel, fixed-dose, haloperidol controlled trial; subjects with schizophrenia or schizoaffective disorder (Ziprasidone: n=73, haloperidol: n=17); ziprasidone doses (2, 5, 20, 80 mg bid).
128-102-US	Four-week, open, ascending dose trial; neuroleptic resistant, chronic schizophrenia (n=13); ziprasidone doses (20, 40, 60, 80 mg bid).
128-104-US	Four-week, double-blind, randomized, fixed-dose, placebo-controlled trial; subjects with schizophrenia or schizoaffective disorder (Ziprasidone: n=150, placebo: n=50); ziprasidone doses (5, 20, 40 mg bid).
128-104E-US	One hundred four-week, double-blind , fixed-dose, placebo-controlled extension trial; subjects with schizophrenia or schizoaffective disorder (Ziprasidone: n=6, placebo: n=1); ziprasidone doses (5, 20, 40 mg bid).
128-105-US	Four to Six week, third party-blind, parallel, placebo-controlled trial; subjects with dementia (Ziprasidone: n=11, pbo: n=12); ziprasidone doses (2-6 mg).
128-106-US	Four-week, double-blind, randomized, fixed-dose, placebo-controlled trial; subjects with schizophrenia or schizoaffective disorder (Ziprasidone: n=91, placebo: n=48); ziprasidone doses (20, 60 mg bid).
128-106E-US	Seventy-six week, double-blind , fixed-dose, placebo-controlled extension trial; subjects with schizophrenia or schizoaffective disorder (Ziprasidone: n=21, placebo: n=8); ziprasidone doses (20 mg bid, 20 mg qd, 60 mg bid, 60 mg qd).
128-109-US	Six-week, double-blind, randomized, fixed-dose, parallel trial; subjects with schizophrenia or schizoaffective disorder (n=35); ziprasidone doses (20 mg qid, 80 mg bid).
128-109E-US	Fifty-two week, open, fixed-dose extension trial; subjects with schizophrenia or schizoaffective disorder (n=6); ziprasidone dose (80 mg qd).
128-110-US	Five-day, open, flexible-dose escalation trial; subjects with psychosis and acute agitation (n=10); ziprasidone dose (20 mg bid to 80 mg bid).
128-111-US	Eight-week, double-blind, randomized, haloperidol-controlled trial; subjects with schizophrenia or schizoaffective disorder and concurrent alcohol/cannabis abuse/dependence (Ziprasidone: n=3, haloperidol: n=6); ziprasidone dose (40 mg bid).
128-114-US	Six-week, double-blind, randomized, fixed-dose, parallel, placebo-controlled trial; subjects with schizophrenia or schizoaffective disorder (Ziprasidone: n=210, placebo: n=92); ziprasidone doses (40, 80 mg bid).
128-115-US	Six-week, double-blind, randomized, fixed-dose, parallel, haloperidol and placebo-controlled trial; subjects with schizophrenia or schizoaffective disorder (Ziprasidone: n=336, haloperidol: n=85, placebo: n=83); ziprasidone doses (20, 60, 100 mg bid).
128-118-US	Four-day, open, flexible-dose trial; subjects with psychosis and acute agitation (n=14); ziprasidone dose (20 mg bid to 120 mg bid).
128-120-South Africa	Five-day, open, non-randomized intramuscular to oral dose trial; subjects with psychosis (n=12); ziprasidone doses (intramuscular: 2.5 to 20 mg bid to qid, oral: 20 to 60 mg bid).
128-303-EU	Fifty-two week, double-blind, randomized, fixed-dose, parallel, placebo-controlled trial; hospitalized subjects with chronic or subchronic schizophrenia (Ziprasidone: n=219, pbo: n=75); ziprasidone doses (20, 40, 80 mg bid).

Appendix 5.1.2.1 Demographics of subjects exposed to ziprasidone in Phase I clinical trial (adapted from sponsor's electronic submission)

Demographic Characteristics
All Clinical Pharmacology Studies

	Ziprasidone			Haloperidol			Other		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects	596	119	715	4	0	4	44	5	49
Age (years):									
<18 years	4	2	6	0	0	0	0	0	0
18-64 years	576	104	680	4	0	4	44	5	49
65-74 years	16	12	28	0	0	0	0	0	0
>=75 years	0	1	1	0	0	0	0	0	0
Mean age (years)	29.5	36.0	30.6	30.0		30.0	27.2	27.0	27.2
Age range	14-74	11-76	11-76	25-40		25-40	18-40	20-37	18-40
Race:									
Asian	5	1	6	0	0	0	2	1	3
Black	69	5	74	0	0	0	4	2	6
Caucasian	458	102	560	4	0	4	33	2	35
Other	64	11	75	0	0	0	5	0	5
Mean weight (kg)	76.0	64.6		79.5			78.0	59.7	
Weight range	49-115	34-92		68-93			57-98	48-69	

(CONTINUED)
The numbers in each treatment group may not match the sum of the IM, IV and ORAL groups in the Route of Administration table, since some subjects are counted in more than one of these groups.
Protocols: 001,002,004,005,006,007,008,009,010,011,013,014,016,017,018,019,020,021,022,023,024,025,026,027,028,029,030,031, 032,033,034,035,036,037,038,039,040,041,043,044,047,048,049,201,202,203

	Placebo		
	Male	Female	Total
Number of Subjects	111	24	135
Age (years):			
<18 years	0	0	0
18-64 years	111	24	135
65-74 years	0	0	0
>=75 years	0	0	0
Mean age (years)	28.0	28.5	28.1
Age range	18-45	22-45	18-45
Race:			
Asian	1	0	1
Black	15	1	16
Caucasian	86	23	109
Other	9	0	9
Mean weight (kg)	76.0	64.8	
Weight range	54-98	50-82	

The numbers in each treatment group may not match the sum of the IM, IV and ORAL groups in the Route of Administration table, since some subjects are counted in more than one of these groups.
Protocols: 001,002,004,005,006,007,008,009,010,011,013,014,016,017,018,019,020,021,022,023,024,025,026,027,028,029,030,031, 032,033,034,035,036,037,038,039,040,041,043,044,047,048,049,201,202,203
Date of Table Generation: 10JAN97

Appendix 5.1.2.2 Demographic profile for Phase II/III trials (adapted from sponsor's submission of 8/29/97)

Demographic Characteristics

All Oral Dosing Phase II/III Studies

	Ziprasidone			Haloperidol			Risperidone		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects	1824	741	2565	391	194	585	203	92	295
Age (years):									
<18 years	15	2	17	0	0	0	0	0	0
18-64 years	1774	711	2485	387	189	576	203	87	290
65-74 years	31	24	55	3	4	7	0	4	4
>=75 years	4	4	8	1	1	2	0	1	1
Mean age (years)	38.1	41.9	39.2	37.2	41.0	38.5	35.7	39.6	36.9
Age range	7-78	11-82	7-82	18-75	18-82	18-82	18-64	18-75	18-75
Race:									
Asian	32	10	42	9	4	13	4	4	8
Black	267	110	377	48	24	72	11	11	22
Caucasian	1403	598	2001	323	163	486	169	76	245
Other	122	23	145	11	3	14	19	1	20
Mean weight (kg)	79.2	72.8		80.0	73.0		82.2	72.6	
Weight range	27-163	35-145		38-149	40-151		48-159	40-123	

(CONTINUED)
Protocols: 015,101,102,104,104E,106,106E,108,108E,109,109E,110,111,114,115,1168,117,118,122,301,302,302E,303,304,304E,305,307
Date of Table Generation: 27JUN97

Four month safety update - cumulative
Demographic Characteristics

All Oral Dosing Phase II/III Studies

	Amisulpride			Placebo		
	Male	Female	Total	Male	Female	Total
Number of Subjects	29	20	49	281	89	370
Age (years):						
<18 years	1	0	1	8	4	12
18-64 years	28	20	48	266	82	348
65-74 years	0	0	0	6	3	9
>=75 years	0	0	0	1	0	1
Mean age (years)	38.0	34.8	36.7	39.1	41.8	39.7
Age range	8-55	24-48	8-55	8-76	10-70	8-76
Race:						
Asian	0	0	0	6	2	8
Black	0	0	0	50	18	68
Caucasian	29	20	49	203	64	267
Other	0	0	0	22	5	27
Mean weight (kg)	74.8	67.4		78.3	70.4	
Weight range	50-103	55-86		25-133	35-118	

Protocols: 015,101,102,104,104E,106,106E,108,108E,109,109E,110,111,114,115,1168,117,118,122,301,302,302E,303,304,304E,305,307
Date of Table Generation: 27JUN97

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Appendix 5.1.3.1 Number of all subjects in phase I trials taking ziprasidone (adapted from sponsor's submission)

Modal Daily Dose and Duration of Ziprasidone Treatment
All Multiple Dose Clinical Pharmacology Studies

	Modal Total Daily Dose Per Subject															
	<40mg		40mg		80mg		120mg		160mg		200mg		240mg		320mg		Total (%)	
Number of Subjects with Treatment Duration																		
<= 1 day	6		2		0		0		0		0		0		0		8	(2.6)
2-7 days	2		70		1		0		0		0		0		0		73	(23.9)
8-14 days	0		122		47		0		0		0		0		0		169	(55.2)
15-28 days	6		14		15		13		8		0		0		0		56	(18.3)
29-60 days	0		0		0		0		0		0		0		0		0	(0.0)
61-90 days	0		0		0		0		0		0		0		0		0	(0.0)
91-180 days	0		0		0		0		0		0		0		0		0	(0.0)
181-360 days	0		0		0		0		0		0		0		0		0	(0.0)
>= 361 days	0		0		0		0		0		0		0		0		0	(0.0)
Number of Subjects (%)	14	(4.6)	208	(68.0)	63	(20.6)	13	(4.2)	8	(2.6)	0	(0.0)	0	(0.0)	0	(0.0)	306	(100.0)
Mean Duration	8		8		13		18		18		0		0		0		10	
Range																		

Subjects with a modal daily dose not represented above are included in the next lowest dose category.
Protocols: 002,005,013,025,026,028,030,035,040,041,043,047,049,203
Date of Table Generation: 10JAN97

Appendix 5.1.3.2 Number of all subjects in phase II/III trial taking ziprasidone (adapted from sponsor's submission)

Four month safety update - cumulative
Modal Daily Dose and Duration of Ziprasidone Treatment
All Oral Dosing Phase II/III Studies

	Modal Total Daily Dose Per Subject															
	<40mg		40mg		80mg		120mg		160mg		200mg		240mg		320mg		Total (%)	
Number of Subjects with Treatment Duration																		
<= 1 day	5		7		2		0		0		0		0		0		14	(0.5)
2-7 days	43		84		77		16		5		1		0		0		226	(8.8)
8-14 days	18		59		86		32		20		13		0		0		228	(8.9)
15-28 days	47		103		126		51		64		26		0		0		417	(16.3)
29-60 days	15		59		182		105		116		74		1		0		552	(21.5)
61-90 days	0		91		62		84		52		88		0		0		377	(14.7)
91-180 days	0		21		101		30		45		21		0		0		218	(8.5)
181-360 days	2		24		126		47		62		20		0		0		281	(11.0)
>= 361 days	1		40		89		28		78		16		0		0		252	(9.8)
Number of Subjects (%)	131	(5.1)	488	(19.0)	851	(33.2)	393	(15.3)	442	(17.2)	259	(10.1)	1	(0.0)	0	(0.0)	2565	(100.0)
Mean Duration	30		80		119		108		156		98		59		0		110	
Range																		

Subjects with a modal daily dose not represented above are included in the next lowest dose category.
Protocols: 015,101,102,104,104E,106,106E,108,108E,109,109E,110,111,114,115,1168,117,118,122,301,302,302E,303,304,304E,305,307
Date of Table Generation: 27JUN97

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Appendix 7.2.1.2
(from Sponsor's Submission)

Subject Disposition
Ziprasidone Protocol 106

Treatment Group	Number of Subjects		Number of Subjects Completing Each Period of Study*			
	Randomized	Treated	Week 1	Week 2	Week 3	Week 4
Ziprasidone, 20 mg BID	44	44	42	39	33	28
Ziprasidone, 60 mg BID	47	47	42	38	28	24
Placebo	48	48	44	38	28	24
Total:	139	139	128	115	89	76

*Based on planned primary efficacy measurements. Weeks are determined by visit designators. Week 1 counts subjects who have at least one primary efficacy measurement at visit 7; Week 2 similarly counts those with visit 14; Week 3 similarly counts those with visit 21; Week 4 similarly counts those with visit 28.
Source Data: Appendix V Tables 6, 15, 16. Date of Data Extraction: 18SEP95. Date of Table Generation: 15JAN96.

Appendix 7.2.1.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 106

	Ziprasidone 20 mg BID			Ziprasidone 60 mg BID			Placebo		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	30	14	44	39	8	47	41	7	48
Age (years):									
18-44	24	7	31	29	2	31	32	4	36
44-64	5	7	12	10	6	16	8	3	11
>=65	1	0	1	0	0	0	1	0	1
Mean age (years)	38.6	44.6	40.5	37.0	47.5	38.8	38.2	43.7	39.0
Age range	25-65	21-60	21-65	19-59	23-57	19-59	21-67	29-57	21-67
Race:									
Caucasian	22	9	31	26	8	34	29	6	35
Black	5	5	10	9	0	9	7	1	8
Oriental	0	0	0	2	0	2	3	0	3
Other	3	0	3	2	0	2	2	0	2
Mean weight (kg)	79.9	67.8		79.0	74.0		80.3	64.5	
Weight range	59-138	41- 91		56-126	44-108		52-108	54- 79	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 05SEP95 Date of Table Generation: 12SEP95

BPRS Total Score Study 106
(from Sponsor's Submission)

BPRS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 106

	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
20 mg BID	43	36.5	42	-3.8	39	-5.4	33	-9.0	28	-8.9
60 mg BID	41	36.6	41	-5.6	38	-7.3	27	-12.4	24	-16.0
Placebo	47	37.0	44	-4.0	37	-6.1	28	-8.0	24	-9.4
	2-Sided P-Values for Pairwise Comparisons									
Ziprasidone 20 mg BID vs placebo		0.838		0.923		0.767		0.395		0.747
Ziprasidone 60 mg BID vs placebo		0.874		0.423		0.373		0.098		0.018

Source Data: Appendix V Table 15. Date of Data Extraction: 15DEC95.
Date of Table Generation: 23MAY96.

BPRS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 106

	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
20 mg BID	43	36.5	43	-3.7	43	-4.9	43	-5.7	43	-5.2
60 mg BID	41	36.6	41	-5.6	41	-7.2	41	-8.2	41	-10.1
Placebo	47	37.0	47	-3.8	47	-4.3	47	-4.0	47	-4.1
	2-Sided P-Values for Pairwise Comparisons									
Ziprasidone 20 mg BID vs placebo		0.838		0.990		0.773		0.468		0.657
Ziprasidone 60 mg BID vs placebo		0.874		0.380		0.208		0.108		0.022

Source Data: Appendix V Table 15. Date of Data Extraction: 15DEC95.
Date of Table Generation: 23MAY96.

BPRS Core Items Study 106
(from Sponsor's Submission)

BPRS Core Items Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 106

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean
				Treatment Week						
Ziprasidone										
20 mg BID	43	13.4	42	-2.1	39	-2.8	33	-4.1	28	-3.6
60 mg BID	41	13.6	41	-2.4	38	-2.9	28	-4.7	24	-5.8
Placebo	47	13.9	44	-2.0	38	-2.0	28	-3.5	24	-3.9
				2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo		0.526		0.645		0.178		0.368		0.619
Ziprasidone 60 mg BID vs placebo		0.661		0.555		0.209		0.210		0.096

Source Data: Appendix V Table 15. Date of Data Extraction: 28JUL95.
Date of Table Generation: 23MAY96.

BPRS Core Items Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 106

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean
				Treatment Week						
Ziprasidone										
20 mg BID	43	13.4	43	-2.0	43	-2.7	43	-3.1	43	-2.6
60 mg BID	41	13.6	41	-2.4	41	-3.0	41	-3.5	41	-4.1
Placebo	47	13.9	47	-2.0	47	-1.9	47	-2.2	47	-2.3
				2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo		0.526		0.812		0.271		0.322		0.677
Ziprasidone 60 mg BID vs placebo		0.661		0.587		0.213		0.186		0.059

Source Data: Appendix V Table 15. Date of Data Extraction: 28JUL95.
Date of Table Generation: 23MAY96.

CGI Severity Score Study 106
(from Sponsor's Submission)

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 106

	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
20 mg BID	43	4.7	42	-0.1	39	-0.5	33	-0.8	28	-0.7
60 mg BID	42	4.7	42	-0.3	38	-0.5	28	-0.8	24	-1.0
Placebo	47	4.7	44	-0.1	38	-0.3	28	-0.3	24	-0.5

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 20 mg BID vs placebo	0.978	0.690	0.105	0.012	0.330
Ziprasidone 60 mg BID vs placebo	0.824	0.215	0.233	0.024	0.033

Source Data: Appendix V Table 16. Date of Data Extraction: 28JUL95.
Date of Table Generation: 23MAY96.

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 106

	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
20 mg BID	43	4.7	43	-0.1	43	-0.4	43	-0.5	43	-0.4
60 mg BID	42	4.7	42	-0.3	42	-0.5	42	-0.5	42	-0.6
Placebo	47	4.7	47	-0.1	47	-0.2	47	-0.1	47	-0.2

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 20 mg BID vs placebo	0.978	0.805	0.169	0.034	0.209
Ziprasidone 60 mg BID vs placebo	0.824	0.167	0.238	0.040	0.039

Source Data: Appendix V Table 16. Date of Data Extraction: 28JUL95.
Date of Table Generation: 23MAY96.

SANS Total Score Study 106
(from Sponsor's Submission)

SANS Total Score - Mean Change from Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 106

Treatment Groups	Treatment Week: Baseline n	Baseline Mean	Week 2 n	Week 2 Mean	Week 4 n	Week 4 Mean
Ziprasidone						
20 mg BID	42	52.2	38	-7.7	26	-11.5
60 mg BID	40	50.9	37	-3.8	22	-14.0
Placebo	42	49.1	34	-2.1	22	-7.6

	2-Sided P-Values for Pairwise Comparisons		
Ziprasidone 20 mg BID vs placebo	0.503	0.166	0.462
Ziprasidone 60 mg BID vs placebo	0.706	0.642	0.204

Source Data: Appendix V Table 17. Date of Data Extraction: 30MAY96.
Date of Table Generation: 31MAY96.

SANS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 106

Treatment Groups	Treatment Week: Baseline n	Baseline Mean	Week 2 n	Week 2 Mean	Week 4 n	Week 4 Mean
Ziprasidone						
20 mg BID	42	52.2	42	-6.5	42	-8.6
60 mg BID	40	50.9	40	-3.6	40	-7.4
Placebo	42	49.1	41	-1.3	42	-2.4

	2-Sided P-Values for Pairwise Comparisons		
Ziprasidone 20 mg BID vs placebo	0.503	0.192	0.165
Ziprasidone 60 mg BID vs placebo	0.706	0.534	0.197

Source Data: Appendix V Table 17. Date of Data Extraction: 30MAY96.
Date of Table Generation: 31MAY96.

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Appendix 7.2.2.2
(from Sponsor's Submission)

Subject Disposition
Ziprasidone Protocol 114

Treatment Group	Number of Subjects		Number of Subjects Completing Each Period of Study*					
	Randomized	Treated	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Ziprasidone, 40 mg BID	106	106	103	94	78	69	57	54
Ziprasidone, 80 mg BID	104	104	103	97	92	80	73	67
Placebo	92	92	88	77	68	58	50	45
Total:	302	302	294	268	238	207	180	166

*Based on planned primary efficacy measurements. Weeks are determined by visit designators. Week 1 counts subjects who have at least one primary efficacy measurement at visit 7; Week 2 similarly counts those with visit 14; Week 3 similarly counts those with visit 21; Week 4 similarly counts those with visit 28; Week 5 similarly counts those with visit 35; Week 6 similarly counts those with visit 42.
Source Data: Appendix V Tables 6, 15, 16. Date of Data Extraction: 29MAR96. Date of Table Generation: 01APR96.

Appendix 7.2.2.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 114

	Ziprasidone 40 mg BID			Ziprasidone 80 mg BID			Placebo		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	75	31	106	77	27	104	63	29	92
Age (years):									
18-44	60	23	83	66	19	85	51	20	71
45-64	14	7	21	11	7	18	12	9	21
>=65	1	1	2	0	1	1	0	0	0
Mean age (years)	35.6	39.6	36.8	34.6	39.1	35.8	35.7	40.4	37.2
Age range	19-65	24-67	19-67	18-58	24-65	18-65	18-63	18-64	18-64
Race:									
White	52	25	77	55	18	73	39	17	56
Black	15	4	19	11	6	17	15	9	24
Asian	1	1	2	3	0	3	2	0	2
Other	7	1	8	8	3	11	7	3	10
Mean weight (kg)	77.9	68.6		78.6	72.0		82.4	73.1	
Weight range	57-137	50-111		49-127	44-101		51-122	49-118	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 26MAR96 Date of Table Generation: 27MAR96

BPRSd Total Score Study 114
(from Sponsor's Submission)

BPRSd Total Score - Mean Change From Baseline and P-Values by Week - All Subjects, Observed Cases
Ziprasidone Protocol 114

	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	56.5	103	-4.1	94	-4.0	78	-9.1	69	-11.6	57	-15.8	54	-15.5
80 mg BID	103	55.0	103	-6.3	96	-8.4	92	-11.2	80	-12.1	73	-13.3	67	-13.9
Placebo	91	55.1	87	-1.1	77	-4.9	68	-6.0	58	-8.5	50	-10.7	45	-12.2

	2-Sided P-Values for Pairwise Comparisons**						
Ziprasidone 40 mg BID vs placebo	0.4521	0.0381	0.6611	0.1020	0.1574	0.0147	0.1747
Ziprasidone 80 mg BID vs placebo	0.9250	0.0001	0.0127	0.0021	0.0315	0.1566	0.4410

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28
Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response
As covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 17APR96.

BPRSd Total Score - Mean Change From Baseline and P-Values by Week - All Subjects, LOCF
Ziprasidone Protocol 114

	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	56.5	104	-4.1	104	-3.4	104	-6.2	104	-7.2	104	-8.0	104	-7.7
80 mg BID	103	55.0	103	-6.3	103	-8.1	103	-10.6	103	-10.5	103	-10.5	103	-10.3
Placebo	91	55.1	90	-0.8	91	-2.6	91	-2.3	91	-2.9	91	-3.2	91	-3.4

	2-Sided P-Values for Pairwise Comparisons**						
Ziprasidone 40 mg BID vs placebo	0.4521	0.0236	0.6489	0.0419	0.0439	0.0240	0.0472
Ziprasidone 80 mg BID vs placebo	0.9250	0.0001	0.0003	0.0001	0.0001	0.0001	0.0003

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28
Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response
As covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 03APR96.

BPRSd Core Items Study 114
(from Sponsor's Submission)

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week - All Subjects, Observed Cases
Ziprasidone Protocol 114

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
						Treatment Week*								
Ziprasidone														
40 mg BID	104	16.9	103	-1.9	94	-2.0	78	-3.6	69	-4.5	57	-5.6	54	-5.9
80 mg BID	103	16.6	103	-2.5	96	-3.7	92	-4.5	80	-5.1	73	-5.8	67	-5.8
Placebo	91	16.4	87	-1.0	77	-2.2	68	-2.6	58	-3.2	50	-4.0	45	-4.5
						2-Sided P-Values for Pairwise Comparisons**								
Ziprasidone 40 mg BID vs placebo		0.3573		0.0380		0.6995		0.1487		0.1123		0.0507		0.1714
Ziprasidone 80 mg BID vs placebo		0.7136		0.0003		0.0045		0.0025		0.0071		0.0088		0.1533

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28
Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response
As covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 02APR96.

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week - All Subjects, LOCF
Ziprasidone Protocol 114

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
						Treatment Week**								
Ziprasidone														
40 mg BID	104	16.9	104	-1.8	104	-1.8	104	-2.7	104	-3.1	104	-3.3	104	-3.4
80 mg BID	103	16.6	103	-2.5	103	-3.5	103	-4.2	103	-4.3	103	-4.5	103	-4.4
Placebo	91	16.4	90	-0.9	91	-1.6	91	-1.6	91	-1.7	91	-1.9	91	-2.0
						2-Sided P-Values for Pairwise Comparisons*								
Ziprasidone 40 mg BID vs placebo		0.3573		0.0256		0.5929		0.0553		0.0260		0.0207		0.0396
Ziprasidone 80 mg BID vs placebo		0.7136		0.0002		0.0002		0.0001		0.0001		0.0001		0.0002

**Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28
Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
*Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response
As covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 01APR96.

CGI Severity Score Study 114
(from Sponsor's Submission)

CGI Severity Score - Mean Change From Baseline and P-Values by Week - All Subjects, Observed Cases
Ziprasidone Protocol 114

	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	4.8	103	-0.3	94	-0.2	78	-0.5	69	-0.6	57	-0.9	54	-1.0
80 mg BID	103	4.8	103	-0.3	97	-0.6	92	-0.7	80	-1.0	73	-1.0	67	-1.1
Placebo	92	4.8	88	-0.1	77	-0.3	68	-0.3	58	-0.5	50	-0.6	45	-0.8

	2-Sided P-Values for Pairwise Comparisons**						
Ziprasidone 40 mg BID vs placebo	0.9477	0.1244	0.9983	0.0677	0.2355	0.0162	0.2157
Ziprasidone 80 mg BID vs placebo	0.5024	0.0166	0.0111	0.0101	0.0010	0.0040	0.0281

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28
Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response
As covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 16. Date of Data Extraction: 29MAR96. Date of Table Generation: 02APR96.

CGI Severity Score - Mean Change From Baseline and P-Values by Week - All Subjects, LOCF
Ziprasidone Protocol 114

	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	4.8	104	-0.3	104	-0.2	104	-0.4	104	-0.4	104	-0.5	104	-0.5
80 mg BID	103	4.8	103	-0.3	103	-0.5	103	-0.6	103	-0.8	103	-0.8	103	-0.8
Placebo	92	4.8	91	-0.1	92	-0.1	92	-0.1	92	-0.2	92	-0.2	92	-0.2

	2-Sided P-Values for Pairwise Comparisons**						
Ziprasidone 40 mg BID vs placebo	0.9477	0.0864	0.6033	0.0324	0.0649	0.0096	0.0299
Ziprasidone 80 mg BID vs placebo	0.5024	0.0115	0.0007	0.0002	0.0001	0.0001	0.0001

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28
Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response
As covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 16. Date of Data Extraction: 29MAR96. Date of Table Generation: 17APR96.

PANSS Total Score Study 114
(from Sponsor's Submission)

PANSS Total Score - Mean Change From Baseline and P-Values by Week - All Subjects, Observed Cases
Ziprasidone Protocol 114

	Treatment Week*						
	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Treatment Groups	n Mean	n Mean	n Mean	n Mean	n Mean	n Mean	n Mean
Ziprasidone							
40 mg BID	104 98.2	103 -7.0	94 -6.5	78 -14.3	69 -18.4	57 -25.3	54 -25.6
80 mg BID	103 95.8	103 -9.9	96 -14.0	92 -18.6	80 -20.2	73 -22.2	67 -23.5
Placebo	91 97.3	86 -1.6	77 -7.7	68 -9.3	58 -13.8	50 -19.0	44 -21.0
	2-Sided P-Values for Pairwise Comparisons**						
Ziprasidone 40 mg BID vs placebo	0.7859	0.0169	0.8971	0.0743	0.1126	0.0265	0.1217
Ziprasidone 80 mg BID vs placebo	0.6324	0.0001	0.0058	0.0005	0.0120	0.1721	0.3418

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28
Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 03APR96.

PANSS Total Score - Mean Change From Baseline and P-Values by Week - All Subjects, LOCF
Ziprasidone Protocol 114

	Treatment Week*						
	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Treatment Groups	n Mean	n Mean	n Mean	n Mean	n Mean	n Mean	n Mean
Ziprasidone							
40 mg BID	104 98.2	104 -6.9	104 -5.5	104 -9.7	104 -11.3	104 -12.6	104 -12.4
80 mg BID	103 95.8	103 -9.9	103 -13.4	103 -17.4	103 -17.2	103 -17.0	103 -17.1
Placebo	91 97.3	89 -1.2	91 -3.8	91 -3.2	91 -4.3	91 -5.0	91 -5.4
	2-Sided P-Values for Pairwise Comparisons**						
Ziprasidone 40 mg BID vs placebo	0.7859	0.0100	0.5010	0.0274	0.0307	0.0250	0.0478
Ziprasidone 80 mg BID vs placebo	0.6324	0.0001	0.0002	0.0001	0.0001	0.0001	0.0002

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28
Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 01APR96.

PANSS Negative Score Study 114
(from Sponsor's Submission)

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week - All Subjects, Observed Cases
Ziprasidone Protocol 114

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
	Treatment Week*													
Ziprasidone														
40 mg BID	104	25.4	103	-2.1	94	-1.9	78	-3.3	69	-3.9	57	-5.7	54	-5.7
80 mg BID	103	24.3	103	-2.4	96	-3.1	92	-4.1	80	-4.7	73	-5.1	67	-5.2
Placebo	91	24.9	86	0.3	77	-1.3	68	-1.7	58	-2.6	50	-5.0	45	-5.4
	2-Sided P-Values for Pairwise Comparisons**													
Ziprasidone 40 mg BID vs placebo	0.6687		0.0004		0.4771		0.1164		0.0615		0.1300		0.2144	
Ziprasidone 80 mg BID vs placebo	0.5793		0.0001		0.0097		0.0016		0.0021		0.4064		0.5720	

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28
Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response
As covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 02APR96.

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week - All Subjects, LOCF
Ziprasidone Protocol 114

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
	Treatment Week**													
Ziprasidone														
40 mg BID	104	25.4	104	-2.1	104	-1.6	104	-2.4	104	-2.7	104	-3.2	104	-3.2
80 mg BID	103	24.3	103	-2.4	103	-3.0	103	-4.0	103	-4.0	103	-3.8	103	-3.9
Placebo	91	24.9	89	0.3	91	-0.3	91	-0.4	91	-0.4	91	-1.0	91	-0.9
	2-Sided P-Values for Pairwise Comparisons*													
Ziprasidone 40 mg BID vs placebo	0.6687		0.0004		0.1566		0.0267		0.0109		0.0238		0.0236	
Ziprasidone 80 mg BID vs placebo	0.5793		0.0001		0.0007		0.0001		0.0001		0.0009		0.0006	

**Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28
Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
*Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response
as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 01APR96.

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Appendix 7.2.3.2
(from Sponsor's Submission)

Subject Disposition
Ziprasidone Protocol 115

Treatment Group	Number of Subjects		Number of Subjects Completing Each Period of Study*					
	Randomized	Treated	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Ziprasidone, 20 mg BID	87	87	84	77	62	57	51	50
Ziprasidone, 60 mg BID	78	78	75	69	62	57	50	39
Ziprasidone, 100 mg BID	86	86	82	77	69	60	57	47
Haloperidol	85	85	77	72	67	58	50	47
Placebo	83	83	77	65	48	35	32	27
Total:	419	419	395	360	308	267	240	210

*Based on planned primary efficacy measurements. Weeks are determined by visit designators. Week 1 counts subjects who have at least one primary efficacy measurement at visit 7; Week 2 similarly counts those with visit 14; Week 3 similarly counts those with visit 21; Week 4 similarly counts those with visit 28; Week 5 similarly counts those with visit 35; Week 6 similarly counts those with visit 42.
Source Data: Appendix V Tables 6, 15, 16. Date of Data Extraction: 22OCT96. Date of Table Generation: 22OCT96.

Appendix 7.2.3.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 115

	Ziprasidone 20 mg BID			Ziprasidone 60 mg BID			Ziprasidone 100 mg BID		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	53	34	87	55	23	78	55	31	86
Age (years):									
18-44	35	25	60	42	15	57	43	20	63
45-64	18	7	25	11	8	19	12	10	22
>=65	0	2	2	2	0	2	0	1	1
Mean age (years)	41.1	39.1	40.3	39.7	40.7	40.0	36.9	40.5	38.2
Age range	22-60	21-68	21-68	21-72	20-58	20-72	19-60	21-71	19-71
Race:									
White	32	23	55	37	17	54	37	21	58
Black	14	9	23	16	5	21	13	8	21
Asian	2	2	4	2	1	3	0	1	1
Other	5	0	5	0	0	0	5	1	6
Mean weight (kg)	78.5	79.9		78.7	78.5		81.9	72.8	
Weight range	54-117	40-125		51-109	45-110		50-130	46-104	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 22OCT96 Date of Table Generation: 22OCT96

Demographic Characteristics
Ziprasidone Protocol 115

	Haloperidol			Placebo		
	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	60	25	85	54	29	83
Age (years):						
18-44	44	18	62	40	20	60
45-64	16	5	21	13	9	22
>=65	0	2	2	1	0	1
Mean age (years)	38.1	40.6	38.8	38.3	40.0	38.9
Age range	18-64	21-69	18-69	18-65	18-56	18-65
Race:						
White	37	18	55	30	20	50
Black	18	6	24	13	6	19
Asian	2	1	3	1	1	2
Other	3	0	3	10	2	12
Mean weight (kg)	84.4	73.6		79.7	75.9	
Weight range	51-141	49-110		51-133	50-112	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 22OCT96 Date of Table Generation: 22OCT96

BPRSd Total Score Study 115
(from Sponsor's Submission)

BPRSd Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 115

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	53.8	84	-3.5	76	-5.0	61	-8.4	57	-9.3	51	-9.0	50	-11.0
60 mg BID	76	51.8	75	-4.1	68	-5.0	62	-6.5	56	-7.7	50	-7.8	39	-10.5
100 mg BID	82	51.8	82	-3.5	77	-5.9	69	-7.1	60	-7.8	57	-7.4	47	-8.3
Haloperidol	82	53.9	77	-5.3	72	-7.5	67	-8.2	58	-11.8	50	-11.3	47	-12.5
Placebo	80	54.3	77	-0.7	64	-2.7	48	-4.5	35	-8.7	32	-8.1	27	-9.6

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.749	0.015	0.111	0.057	0.598	0.824	0.717
Ziprasidone 60 mg BID vs placebo	0.096	0.004	0.096	0.241	0.758	0.929	0.757
Ziprasidone 100 mg BID vs placebo	0.095	0.011	0.024	0.187	0.987	0.907	0.741
Haloperidol vs placebo	0.754	0.000	0.004	0.228	0.275	0.254	0.363

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

BPRSd Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 115

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	53.8	86	-3.3	86	-3.6	86	-5.5	86	-5.2	86	-4.2	86	-4.9
60 mg BID	76	51.8	76	-4.0	76	-4.4	76	-4.8	76	-4.8	76	-4.8	76	-5.2
100 mg BID	82	51.8	82	-3.5	82	-5.1	82	-5.4	82	-5.5	82	-5.0	82	-5.2
Haloperidol	82	53.9	82	-4.9	82	-6.7	82	-7.2	82	-8.9	82	-8.5	82	-8.8
Placebo	80	54.3	78	-0.9	80	-1.6	80	-1.6	80	-1.9	80	-1.4	80	-1.2

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.749	0.038	0.166	0.026	0.070	0.129	0.049
Ziprasidone 60 mg BID vs placebo	0.096	0.004	0.030	0.035	0.073	0.048	0.020
Ziprasidone 100 mg BID vs placebo	0.095	0.020	0.013	0.020	0.040	0.041	0.023
Haloperidol vs placebo	0.754	0.001	0.001	0.003	0.000	0.000	0.000

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 27SEP96.

BPRSd Core Items Study 115
(from Sponsor's Submission)

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 115

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
						Treatment Week								
Ziprasidone														
20 mg BID	86	16.1	84	-1.5	76	-2.0	61	-2.9	57	-3.1	51	-3.3	50	-3.9
60 mg BID	76	16.0	75	-1.5	68	-1.9	62	-2.7	56	-3.1	50	-2.8	39	-3.9
100 mg BID	82	15.9	82	-1.6	77	-2.5	69	-3.3	60	-3.5	57	-3.6	47	-4.1
Haloperidol	82	16.2	77	-2.3	72	-3.2	67	-3.7	58	-4.8	50	-4.6	47	-5.2
Placebo	80	16.6	77	-0.9	64	-1.9	48	-2.2	35	-3.7	32	-4.3	27	-3.9

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.326	0.133	0.767	0.389	0.534	0.269	0.985
Ziprasidone 60 mg BID vs placebo	0.225	0.130	0.848	0.447	0.512	0.127	0.819
Ziprasidone 100 mg BID vs placebo	0.146	0.069	0.208	0.132	0.990	0.594	0.578
Haloperidol vs placebo	0.459	0.002	0.017	0.078	0.227	0.595	0.119

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 115

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
						Treatment Week								
Ziprasidone														
20 mg BID	86	16.1	86	-1.4	86	-1.5	86	-2.2	86	-2.1	86	-2.1	86	-2.3
60 mg BID	76	16.0	76	-1.5	76	-1.8	76	-2.1	76	-2.2	76	-2.0	76	-2.2
100 mg BID	82	15.9	82	-1.6	82	-2.2	82	-2.5	82	-2.4	82	-2.3	82	-2.6
Haloperidol	82	16.2	82	-2.2	82	-3.0	82	-3.4	82	-4.0	82	-3.9	82	-4.1
Placebo	80	16.6	78	-0.9	80	-1.4	80	-1.0	80	-1.2	80	-1.3	80	-0.9

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.326	0.196	0.636	0.039	0.103	0.206	0.034
Ziprasidone 60 mg BID vs placebo	0.225	0.167	0.339	0.051	0.083	0.252	0.046
Ziprasidone 100 mg BID vs placebo	0.146	0.101	0.099	0.010	0.044	0.113	0.009
Haloperidol vs placebo	0.459	0.005	0.004	0.000	0.000	0.000	0.000

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

CGI Severity Score Study 115
(from Sponsor's Submission)

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 115

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	4.9	84	-0.1	77	-0.3	62	-0.5	57	-0.7	51	-0.8	50	-0.8
60 mg BID	76	4.9	75	-0.2	69	-0.4	62	-0.5	57	-0.6	50	-0.6	39	-0.8
100 mg BID	83	4.7	82	-0.1	77	-0.4	69	-0.5	60	-0.6	57	-0.6	47	-0.7
Haloperidol	83	5.0	77	-0.4	72	-0.7	67	-0.8	58	-0.9	50	-1.0	47	-1.1
Placebo	80	4.9	77	-0.1	65	-0.2	48	-0.4	35	-0.5	32	-0.5	27	-0.7

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.897	0.598	0.574	0.430	0.224	0.354	0.703
Ziprasidone 60 mg BID vs placebo	0.746	0.069	0.103	0.197	0.298	0.677	0.582
Ziprasidone 100 mg BID vs placebo	0.155	0.154	0.012	0.277	0.205	0.407	0.508
Haloperidol vs placebo	0.700	0.001	0.000	0.054	0.032	0.069	0.066

Source Data: Appendix V Table 16. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 115

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	4.9	86	-0.1	86	-0.2	86	-0.3	86	-0.4	86	-0.4	86	-0.4
60 mg BID	76	4.9	76	-0.2	76	-0.3	76	-0.4	76	-0.4	76	-0.4	76	-0.4
100 mg BID	83	4.7	83	-0.1	83	-0.4	83	-0.3	83	-0.4	83	-0.4	83	-0.4
Haloperidol	83	5.0	83	-0.4	83	-0.6	83	-0.7	83	-0.8	83	-0.8	83	-0.8
Placebo	80	4.9	78	-0.1	80	-0.1	80	-0.1	80	-0.0	80	-0.1	80	-0.1

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.897	0.730	0.295	0.043	0.010	0.014	0.030
Ziprasidone 60 mg BID vs placebo	0.746	0.123	0.020	0.011	0.007	0.030	0.035
Ziprasidone 100 mg BID vs placebo	0.155	0.354	0.004	0.008	0.007	0.015	0.006
Haloperidol vs placebo	0.700	0.004	0.000	0.000	0.000	0.000	0.000

Source Data: Appendix V Table 16. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

PANSS Total Score Study 115
(from Sponsor's Submission)

PANSS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 115

	Treatment Week											
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	93.2	84	-5.1	76	-8.0	61	-13.3	57	-14.3	51	-14.2	50	-17.3
60 mg BID	76	90.4	75	-6.3	68	-8.5	62	-11.2	56	-13.4	50	-12.4	39	-18.0
100 mg BID	82	89.5	82	-5.3	77	-9.1	69	-11.4	60	-12.2	57	-11.6	47	-14.0
Haloperidol	82	94.1	77	-8.6	72	-12.4	67	-13.7	58	-20.4	50	-18.9	47	-21.0
Placebo	80	93.3	77	-0.3	64	-4.4	48	-6.1	35	-13.2	32	-12.8	27	-13.9

	2-Sided P-Values for Pairwise Comparisons					
Ziprasidone 20 mg BID vs placebo	0.973	0.019	0.152	0.049	0.648	0.943	0.585
Ziprasidone 60 mg BID vs placebo	0.293	0.003	0.120	0.140	0.982	0.738	0.473
Ziprasidone 100 mg BID vs placebo	0.154	0.009	0.055	0.121	0.920	0.806	0.850
Haloperidol vs placebo	0.762	0.000	0.007	0.130	0.129	0.229	0.187

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

PANSS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 115

	Treatment Week											
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	93.2	86	-4.8	86	-5.6	86	-8.6	86	-8.0	86	-6.6	86	-7.5
60 mg BID	76	90.4	76	-6.3	76	-7.5	76	-8.3	76	-8.3	76	-7.5	76	-8.6
100 mg BID	82	89.5	82	-5.3	82	-7.8	82	-8.5	82	-8.4	82	-7.8	82	-8.3
Haloperidol	82	94.1	82	-8.2	82	-10.9	82	-12.2	82	-15.6	82	-14.5	82	-15.2
Placebo	80	93.3	78	-0.4	80	-1.9	80	-1.1	80	-1.8	80	-1.2	80	-0.4

	2-Sided P-Values for Pairwise Comparisons					
Ziprasidone 20 mg BID vs placebo	0.973	0.041	0.156	0.013	0.051	0.107	0.031
Ziprasidone 60 mg BID vs placebo	0.293	0.004	0.022	0.012	0.032	0.051	0.011
Ziprasidone 100 mg BID vs placebo	0.154	0.017	0.021	0.012	0.032	0.041	0.012
Haloperidol vs placebo	0.762	0.001	0.001	0.001	0.000	0.000	0.000

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

PANSS Negative Score Study 115
(from Sponsor's Submission)

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 115

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	22.9	84	-0.9	76	-1.6	61	-2.5	57	-2.6	51	-2.9	50	-3.7
60 mg BID	76	23.4	75	-1.2	68	-1.8	62	-2.4	56	-3.5	50	-2.6	39	-4.9
100 mg BID	82	22.5	82	-1.3	77	-1.7	69	-2.6	60	-2.5	57	-2.4	47	-3.3
Haloperidol	82	24.1	77	-1.5	72	-2.0	67	-2.6	58	-4.1	50	-3.7	47	-4.2
Placebo	80	22.4	77	0.9	64	-0.2	48	-0.4	35	-2.5	32	-2.0	27	-2.3

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.627	0.016	0.114	0.050	0.794	0.780	0.553
Ziprasidone 60 mg BID vs placebo	0.334	0.012	0.193	0.128	0.746	0.844	0.244
Ziprasidone 100 mg BID vs placebo	0.950	0.005	0.089	0.043	0.866	0.905	0.591
Haloperidol vs placebo	0.089	0.007	0.165	0.196	0.488	0.555	0.562

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 115

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	22.9	86	-0.8	86	-1.1	86	-1.6	86	-1.3	86	-1.1	86	-1.5
60 mg BID	76	23.4	76	-1.2	76	-1.6	76	-1.8	76	-2.1	76	-1.5	76	-2.1
100 mg BID	82	22.5	82	-1.3	82	-1.7	82	-2.1	82	-2.0	82	-2.0	82	-2.2
Haloperidol	82	24.1	82	-1.5	82	-1.9	82	-2.5	82	-3.1	82	-2.8	82	-3.1
Placebo	80	22.4	78	0.8	80	0.3	80	0.5	80	0.0	80	0.2	80	0.2

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.627	0.032	0.168	0.026	0.206	0.261	0.121
Ziprasidone 60 mg BID vs placebo	0.334	0.016	0.077	0.025	0.064	0.204	0.069
Ziprasidone 100 mg BID vs placebo	0.950	0.006	0.039	0.005	0.041	0.039	0.020
Haloperidol vs placebo	0.089	0.008	0.050	0.006	0.010	0.017	0.008

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

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Appendix 7.2.4.2
(from Sponsor's Submission)

Subject Disposition
Ziprasidone Protocol 303

Treatment Group	Number of Subjects		Number of Subjects Completing Each Period of Study*					
	Randomized	Treated	Week 3	Week 6	Week 16	Week 28	Week 40	Week 52
Ziprasidone, 20 mg BID	76	76	67	61	48	40	38	35
Ziprasidone, 40 mg BID	72	72	66	58	47	36	33	33
Ziprasidone, 80 mg BID	71	71	68	66	50	42	36	34
Placebo	75	75	70	56	31	23	16	14
Total:	294	294	271	241	176	141	123	116

*Based on planned scheduled efficacy measurements of PANSS and CGI severity. Weeks are determined by visit designators.
Source Data: Appendix V Tables 6, 15, 16. Date of Data Extraction: 06JAN97. Date of Table Generation: 06JAN97.

Appendix 7.2.4.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 303

	Ziprasidone 20 mg BID			Ziprasidone 40 mg BID			Ziprasidone 80 mg BID			Placebo		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	56	20	76	51	21	72	46	25	71	61	14	75
Age (years):												
18-44	23	6	29	29	3	32	20	7	27	27	3	30
45-64	24	8	32	20	10	30	21	14	35	29	8	37
>=65	9	6	15	2	8	10	5	4	9	5	3	8
Mean age (years)	49.1	55.5	50.8	45.4	59.4	49.5	48.4	52.0	49.6	47.7	53.7	48.8
Age range	18-75	31-82	18-82	24-75	36-78	24-78	22-72	23-73	22-73	20-76	29-70	20-76
Race:												
White	56	20	76	51	21	72	46	25	71	61	14	75
Mean weight (kg)	73.0	72.3		72.3	66.7		73.8	67.3		74.7	65.1	
Weight range	45-124	57-106		49-112	45- 95		51-155	44- 96		54-115	48- 90	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 03JAN97 Date of Table Generation: 06JAN97

Analysis of Time-to-Relapse - All Subjects
Ziprasidone Protocol 303

Treatment Group	N	Cumulative Incidence(%) of Relapse* <=28 weeks	Cumulative Incidence(%) of Relapse* <=52 weeks	Probability of Relapse** <=28 weeks	Probability of Relapse** <=52 weeks	Relative Risk	95% Confidence Limits Lower	95% Confidence Limits Upper	P-Value***
Ziprasidone									
20 mg BID	75	23 (30.7)	27 (36.0)	0.339	0.405	0.481	0.296	0.781	0.003
40 mg BID	72	21 (29.2)	22 (30.6)	0.326	0.346	0.414	0.247	0.693	0.001
80 mg BID	71	22 (31.0)	24 (33.8)	0.324	0.358	0.411	0.249	0.680	0.001
Placebo	75	35 (46.7)	43 (57.3)	0.545	0.708				
Overall									<0.001
Dose Response									0.002
Zip. vs Placebo									<0.001
Linear Among Zip.									0.595

* Percent to number of patients at baseline
** Estimates of probability of relapse at <=28 weeks or <=52 weeks are based on the Kaplan-Meier product-limit method.
***The p-values for comparing each treatment with placebo and for overall are derived from a Cox regression model that includes a contrast variable for each treatment group versus placebo. The p-value for dose response is based on Cox regression model using the actual dosage levels (0 mg for placebo). The dose response is further tested for Ziprasidone groups combined versus placebo using model contrasts (-3,1,1,1) and for linear effect among the Ziprasidone groups using contrasts (0,-1,0,1).

Source Data: Appendix III Table 27. Date of Data Extraction: 06JAN97. Date of Table Generation: 06FEB97.

BPRSd Total Score Study 303
(from Sponsor's Submission)

BPRSd Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	46.1	67	-1.7	60	-4.3	48	-5.4	40	-5.8	38	-7.5	35	-9.3
40 mg BID	72	47.1	66	-2.1	58	-2.8	47	-5.4	36	-6.4	33	-7.1	33	-8.0
80 mg BID	71	45.9	68	-2.2	66	-3.6	50	-4.7	42	-7.7	36	-8.6	34	-9.2
Placebo	75	48.0	70	-0.2	56	-2.9	31	-5.5	23	-4.1	16	-3.0	14	-3.4

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.302	0.120	0.068	0.265	0.056	0.127	0.543
Ziprasidone 40 mg BID vs placebo	0.615	0.073	0.869	0.261	0.053	0.444	0.768
Ziprasidone 80 mg BID vs placebo	0.272	0.053	0.425	0.723	0.002	0.034	0.487

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

BPRSd Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	46.1	75	0.2	75	-0.1	75	1.6	75	3.1	75	2.6	75	2.5
40 mg BID	72	47.1	72	-0.1	72	0.2	72	0.7	72	2.2	72	2.3	72	1.9
80 mg BID	71	45.9	71	-1.5	71	-2.0	71	-0.1	71	0.0	71	0.7	71	0.5
Placebo	75	48.0	75	1.0	75	1.7	75	4.4	75	7.1	75	9.3	75	9.6

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.302	0.546	0.265	0.158	0.041	0.001	0.001
Ziprasidone 40 mg BID vs placebo	0.615	0.544	0.556	0.139	0.035	0.004	0.002
Ziprasidone 80 mg BID vs placebo	0.272	0.083	0.042	0.043	0.001	<0.001	<0.001

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

BPRSd Core Items Study 303
(from Sponsor's Submission)

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 303

Treatment Groups	Baseline n	Baseline Mean	Week 3 n	Week 3 Mean	Week 6 n	Week 6 Mean	Week 16 n	Week 16 Mean	Week 28 n	Week 28 Mean	Week 40 n	Week 40 Mean	Week 52 n	Week 52 Mean
Ziprasidone														
20 mg BID	75	11.2	67	-0.3	60	-1.0	48	-1.1	40	-1.3	38	-1.6	35	-2.3
40 mg BID	72	11.7	66	-0.6	58	-0.8	47	-1.3	36	-1.6	33	-2.0	33	-2.0
80 mg BID	71	11.2	68	-0.6	66	-0.6	50	-1.3	42	-1.8	36	-2.2	34	-2.1
Placebo	75	11.7	70	0.1	56	-0.6	31	-1.5	23	-0.7	16	-0.6	14	-0.2

2-Sided P-Values for Pairwise Comparisons							
Ziprasidone 20 mg BID vs placebo	0.378	0.259	0.127	0.844	0.098	0.458	0.602
Ziprasidone 40 mg BID vs placebo	0.980	0.062	0.567	0.534	0.070	0.468	0.900
Ziprasidone 80 mg BID vs placebo	0.446	0.071	0.742	0.832	0.003	0.074	0.430

Source Data: Appendix V Table 15, Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 303

Treatment Groups	Baseline n	Baseline Mean	Week 3 n	Week 3 Mean	Week 6 n	Week 6 Mean	Week 16 n	Week 16 Mean	Week 28 n	Week 28 Mean	Week 40 n	Week 40 Mean	Week 52 n	Week 52 Mean
Ziprasidone														
20 mg BID	75	11.2	75	0.3	75	0.3	75	0.8	75	1.2	75	1.3	75	1.3
40 mg BID	72	11.7	72	-0.1	72	-0.0	72	0.1	72	0.5	72	0.5	72	0.5
80 mg BID	71	11.2	71	-0.4	71	-0.3	71	0.2	71	0.3	71	0.4	71	0.5
Placebo	75	11.7	75	0.3	75	0.5	75	1.2	75	2.1	75	2.5	75	2.6

2-Sided P-Values for Pairwise Comparisons							
Ziprasidone 20 mg BID vs placebo	0.378	0.919	0.629	0.472	0.168	0.043	0.043
Ziprasidone 40 mg BID vs placebo	0.980	0.438	0.498	0.132	0.035	0.008	0.007
Ziprasidone 80 mg BID vs placebo	0.446	0.146	0.169	0.135	0.010	0.002	0.003

Source Data: Appendix V Table 15, Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

CGI Severity Score Study 303
(from Sponsor's Submission)

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 303

Treatment Groups	Baseline n	Baseline Mean	Week 3 n	Week 3 Mean	Week 6 n	Week 6 Mean	Week 16 n	Week 16 Mean	Week 28 n	Week 28 Mean	Week 40 n	Week 40 Mean	Week 52 n	Week 52 Mean
						Treatment Week								
Ziprasidone														
20 mg BID	75	4.0	67	-0.1	60	-0.2	48	-0.4	40	-0.4	38	-0.5	35	-0.7
40 mg BID	72	4.0	66	-0.0	58	-0.2	47	-0.4	36	-0.6	33	-0.6	33	-0.8
80 mg BID	71	4.0	68	-0.1	66	-0.2	50	-0.4	42	-0.5	36	-0.6	34	-0.7
Placebo	75	4.1	70	0.1	56	-0.2	31	-0.4	23	-0.3	16	-0.3	14	-0.4
						2-Sided P-Values for Pairwise Comparisons								
Ziprasidone 20 mg BID vs placebo		0.724		0.050		0.360		0.608		0.116		0.503		0.853
Ziprasidone 40 mg BID vs placebo		0.557		0.123		0.581		0.278		0.019		0.521		0.683
Ziprasidone 80 mg BID vs placebo		0.733		0.055		0.363		0.569		0.004		0.183		0.493

Source Data: Appendix V Table 16, Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 303

Treatment Groups	Baseline n	Baseline Mean	Week 3 n	Week 3 Mean	Week 6 n	Week 6 Mean	Week 16 n	Week 16 Mean	Week 28 n	Week 28 Mean	Week 40 n	Week 40 Mean	Week 52 n	Week 52 Mean
						Treatment Week								
Ziprasidone														
20 mg BID	75	4.0	75	0.1	75	0.1	75	0.2	75	0.4	75	0.3	75	0.4
40 mg BID	72	4.0	72	0.1	72	0.1	72	0.1	72	0.2	72	0.2	72	0.2
80 mg BID	71	4.0	71	-0.0	71	-0.1	71	0.1	71	0.1	71	0.2	71	0.2
Placebo	75	4.1	75	0.2	75	0.3	75	0.5	75	0.8	75	0.9	75	0.9
						2-Sided P-Values for Pairwise Comparisons								
Ziprasidone 20 mg BID vs placebo		0.724		0.226		0.165		0.041		0.013		0.001		0.001
Ziprasidone 40 mg BID vs placebo		0.557		0.389		0.282		0.011		0.002		<0.001		<0.001
Ziprasidone 80 mg BID vs placebo		0.733		0.049		0.008		0.006		<0.001		<0.001		<0.001

Source Data: Appendix V Table 16, Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

CGI Improvement Score Study 303
(from Sponsor's Submission)

CGI Improvement Score - Means and P-Values by Week
All Subjects, Observed Cases
Ziprasidone Protocol 303

	Treatment Week											
	Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone												
20 mg BID	67	3.5	60	3.4	48	3.1	40	3.2	38	3.1	35	2.7
40 mg BID	66	3.6	58	3.6	47	3.2	36	3.0	33	2.8	33	2.7
80 mg BID	68	3.6	66	3.5	50	3.3	42	2.9	36	2.8	34	2.6
Placebo	70	3.9	56	3.5	31	3.3	23	3.3	16	3.3	14	3.1

	2-Sided P-Values for Pairwise Comparisons					
Ziprasidone 20 mg BID vs placebo	0.019	0.303	0.303	0.118	0.403	0.268
Ziprasidone 40 mg BID vs placebo	0.040	0.866	0.189	0.079	0.462	0.819
Ziprasidone 80 mg BID vs placebo	0.059	0.902	0.553	0.007	0.069	0.204

Source Data: Appendix V Table 16. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

CGI Improvement Score - Means and P-Values by Week
All Subjects, LOCF
Ziprasidone Protocol 303

	Treatment Week											
	Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone												
20 mg BID	75	3.7	75	3.8	75	4.0	75	4.2	75	4.3	75	4.2
40 mg BID	72	3.8	72	3.9	72	3.9	72	4.1	72	4.1	72	4.0
80 mg BID	71	3.7	71	3.7	71	3.9	71	3.9	71	4.0	71	3.9
Placebo	75	4.0	75	4.1	75	4.6	75	4.8	75	5.0	75	5.0

	2-Sided P-Values for Pairwise Comparisons					
Ziprasidone 20 mg BID vs placebo	0.097	0.182	0.015	0.025	0.004	0.001
Ziprasidone 40 mg BID vs placebo	0.231	0.488	0.014	0.009	0.001	0.001
Ziprasidone 80 mg BID vs placebo	0.109	0.089	0.012	0.001	<0.001	<0.001

Source Data: Appendix V Table 16. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

PANSS Total Score Study 303
(from Sponsor's Submission)

PANSS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 303

	Treatment Week											
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	85.1	67	-3.2	60	-7.7	48	-10.1	40	-11.1	38	-14.2	35	-17.8
40 mg BID	72	86.6	66	-4.0	58	-4.9	47	-9.1	36	-12.0	33	-13.7	33	-14.7
80 mg BID	71	85.2	68	-3.5	66	-5.7	50	-9.1	42	-14.2	36	-15.4	34	-17.0
Placebo	75	88.9	70	-1.2	56	-5.9	31	-10.3	23	-8.6	16	-6.5	14	-6.9

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.210	0.150	0.127	0.311	0.057	0.134	0.277
Ziprasidone 40 mg BID vs placebo	0.449	0.083	0.664	0.513	0.066	0.483	0.821
Ziprasidone 80 mg BID vs placebo	0.227	0.135	0.962	0.849	0.002	0.070	0.350

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

PANSS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 303

	Treatment Week											
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	85.1	75	-0.2	75	-1.0	75	1.4	75	3.7	75	2.9	75	2.4
40 mg BID	72	86.6	72	-0.4	72	0.2	72	0.8	72	2.5	72	2.6	72	2.1
80 mg BID	71	85.2	71	-2.7	71	-3.6	71	-1.7	71	-1.5	71	-0.5	71	-1.1
Placebo	75	88.9	75	1.0	75	1.7	75	6.2	75	10.2	75	14.1	75	14.6

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.210	0.591	0.285	0.143	0.041	0.001	0.001
Ziprasidone 40 mg BID vs placebo	0.449	0.621	0.751	0.187	0.042	0.003	0.002
Ziprasidone 80 mg BID vs placebo	0.227	0.110	0.065	0.025	0.001	<0.001	<0.001

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

PANSS Negative Score Study 303
(from Sponsor's Submission)

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	24.9	67	-1.4	60	-2.5	48	-3.4	40	-3.9	38	-4.8	35	-5.6
40 mg BID	72	24.7	66	-1.2	58	-1.4	47	-2.8	36	-3.7	33	-4.4	33	-4.2
80 mg BID	71	25.0	68	-1.3	66	-1.8	50	-3.1	42	-4.6	36	-5.1	34	-5.6
Placebo	75	25.7	70	-1.4	56	-2.3	31	-3.4	23	-3.7	16	-2.8	14	-3.0

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.326	0.715	0.429	0.457	0.249	0.277	0.455
Ziprasidone 40 mg BID vs placebo	0.253	0.928	0.162	0.857	0.479	0.817	0.433
Ziprasidone 80 mg BID vs placebo	0.401	0.920	0.469	0.974	0.063	0.290	0.487

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	24.9	75	-0.9	75	-1.3	75	-1.4	75	-1.4	75	-1.8	75	-2.0
40 mg BID	72	24.7	72	-0.4	72	-0.4	72	-0.8	72	-0.9	72	-1.1	72	-1.0
80 mg BID	71	25.0	71	-1.4	71	-1.7	71	-2.0	71	-2.3	71	-2.3	71	-2.6
Placebo	75	25.7	75	-0.7	75	-0.6	75	0.1	75	0.5	75	1.2	75	1.3

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.326	0.673	0.272	0.039	0.012	<0.001	<0.001
Ziprasidone 40 mg BID vs placebo	0.253	0.750	0.767	0.246	0.082	0.009	0.012
Ziprasidone 80 mg BID vs placebo	0.401	0.203	0.118	0.007	0.001	<0.001	<0.001

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 25FEB97.

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Appendix 7.2.5.2
(from Sponsor's Submission)

Subject Disposition
Ziprasidone Protocol 104

Treatment Group	Number of Subjects		Number of Subjects Completing Each Period of Study*			
	Randomized	Treated	Week 1	Week 2	Week 3	Week 4
Ziprasidone, 5 mg BID	47	47	45	37	33	30
Ziprasidone, 20 mg BID	55	55	54	46	38	27
Ziprasidone, 40 mg BID	48	48	42	32	24	20
Placebo	50	50	45	34	29	27
Total:	200	200	186	149	124	104

*Based on planned primary efficacy measurements. Weeks are determined by visit designators. Week 1 counts subjects who have at least one primary efficacy measurement at visit 7; Week 2 similarly counts those with visit 14; Week 3 similarly counts those with visit 21; Week 4 similarly counts those with visit 28.
Source Data: Appendix V Tables 6, 16, 17. Date of Data Extraction: 17JUL95. Date of Table Generation: 090CT96.

Appendix 7.2.5.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 104

	Ziprasidone 5mg BID			Ziprasidone 20mg BID			Ziprasidone 40mg BID			Placebo		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	41	6	47	52	3	55	39	9	48	44	6	50
Age (years):												
18-44	31	2	33	39	1	40	32	3	35	33	1	34
45-64	10	4	14	13	2	15	7	6	13	11	5	16
Mean age (years)	38.4	44.7	39.2	40.4	51.7	41.1	37.5	49.0	39.7	38.5	47.8	39.6
Age range	22-60	24-57	22-60	25-64	44-56	25-64	20-61	39-63	20-63	22-64	37-56	22-64
Race:												
Caucasian	20	3	23	27	3	30	22	5	27	27	3	30
Black	17	3	20	19	0	19	12	4	16	15	2	17
Oriental	1	0	1	2	0	2	3	0	3	0	1	1
Other	3	0	3	4	0	4	2	0	2	2	0	2
Mean weight (kg)	77.5	71.3		76.8	65.8		76.9	69.4		79.5	67.8	
Weight range	52-120	56-100		55-115	63- 70		49-115	55- 93		58-113	57- 81	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 02AUG95 Date of Table Generation: 29AUG95

BPRS Total Score Study 104
(from Sponsor's Submission)

BPRS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 104

Treatment Groups	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
5 mg BID	44	34.1	44	-2.3	37	-4.3	33	-7.5	30	-7.8
20 mg BID	55	34.5	54	-3.9	46	-4.9	38	-9.2	27	-13.0
40 mg BID	47	36.2	42	-3.4	32	-4.3	24	-8.9	20	-7.3
Placebo	47	33.4	45	-3.6	34	-4.4	29	-7.9	27	-7.3

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.738	0.454	0.667	0.845	0.646
Ziprasidone 20 mg BID vs placebo	0.586	0.894	0.551	0.352	0.040
Ziprasidone 40 mg BID vs placebo	0.185	0.836	0.821	0.446	0.720

Source Data: Appendix V Table 16. Date of Data Extraction: 17JUL95.
Date of Table Generation: 11OCT96.

BPRS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 104

Treatment Groups	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
5 mg BID	44	34.1	44	-2.3	44	-2.8	44	-4.3	44	-3.9
20 mg BID	55	34.5	55	-3.9	55	-3.6	55	-4.9	55	-5.4
40 mg BID	47	36.2	47	-3.0	47	-3.1	47	-3.7	47	-2.6
Placebo	47	33.4	46	-3.3	47	-2.4	47	-3.3	47	-3.5

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.738	0.445	0.923	0.692	0.926
Ziprasidone 20 mg BID vs placebo	0.586	0.828	0.573	0.438	0.354
Ziprasidone 40 mg BID vs placebo	0.185	0.590	0.831	0.989	0.535

Source Data: Appendix V Table 16. Date of Data Extraction: 17JUL95.
Date of Table Generation: 11OCT96.

BPRS Core Items Study 104
(from Sponsor's Submission)

BPRS Core Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 104

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean
				Treatment Week						
Ziprasidone										
5 mg BID	44	12.8	44	-0.9	37	-1.6	33	-2.5	30	-2.9
20 mg BID	55	13.0	54	-1.6	46	-2.8	38	-4.1	27	-5.1
40 mg BID	47	12.8	42	-0.7	32	-0.8	24	-2.5	20	-2.9
Placebo	47	13.7	45	-2.2	34	-2.7	29	-3.8	27	-3.2

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.201	0.062	0.313	0.556	0.491
Ziprasidone 20 mg BID vs placebo	0.299	0.398	0.761	0.341	0.022
Ziprasidone 40 mg BID vs placebo	0.201	0.042	0.090	0.978	0.292

Source Data: Appendix V Table 16. Date of Data Extraction: 17JUL95.
Date of Table Generation: 11OCT96.

BPRS Core Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 104

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean
				Treatment Week						
Ziprasidone										
5 mg BID	44	12.8	44	-0.9	44	-1.3	44	-1.6	44	-1.8
20 mg BID	55	13.0	55	-1.6	55	-2.0	55	-2.3	55	-2.3
40 mg BID	47	12.8	47	-0.7	47	-0.6	47	-1.2	47	-1.2
Placebo	47	13.7	46	-2.0	47	-2.1	47	-2.3	47	-2.2

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.201	0.083	0.252	0.449	0.742
Ziprasidone 20 mg BID vs placebo	0.299	0.593	0.974	0.981	0.751
Ziprasidone 40 mg BID vs placebo	0.201	0.040	0.051	0.193	0.301

Source Data: Appendix V Table 16. Date of Data Extraction: 17JUL95.
Date of Table Generation: 11OCT96.

CGI Severity Score Study 104
(from Sponsor's Submission)

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 104

	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
5 mg BID	46	4.9	45	-0.1	37	-0.1	33	-0.2	30	-0.3
20 mg BID	55	4.8	54	-0.2	46	-0.3	38	-0.6	27	-0.8
40 mg BID	47	4.9	42	-0.2	32	-0.2	24	-0.3	20	-0.4
Placebo	47	5.0	45	-0.3	33	-0.3	29	-0.7	27	-0.7

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.492	0.143	0.444	0.055	0.333
Ziprasidone 20 mg BID vs placebo	0.241	0.604	0.985	0.802	0.293
Ziprasidone 40 mg BID vs placebo	0.788	0.313	0.453	0.232	0.595

Source Data: Appendix V Table 17. Date of Data Extraction: 17JUL95
Date of Table Generation: 11OCT96.

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 104

	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
5 mg BID	46	4.9	46	-0.1	46	-0.0	46	-0.0	46	-0.1
20 mg BID	55	4.8	55	-0.2	55	-0.2	55	-0.3	55	-0.3
40 mg BID	47	4.9	47	-0.1	47	-0.1	47	-0.1	47	-0.2
Placebo	47	5.0	46	-0.3	47	-0.2	47	-0.4	47	-0.4

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.492	0.147	0.283	0.043	0.076
Ziprasidone 20 mg BID vs placebo	0.241	0.723	0.784	0.784	0.827
Ziprasidone 40 mg BID vs placebo	0.788	0.149	0.337	0.143	0.233

Source Data: Appendix V Table 17. Date of Data Extraction: 17JUL95.
Date of Table Generation: 11OCT96.

Appendix Table 8.1.1.1
Deaths occurring during or after trial treatment : Cut-off date: 5/15/97

Ziprasidone subjects who died ≤ 30 days after treatment

SUBJECT #	AGE / SEX	LAST DOSE (MG/D)	DAYS OF TREAT-MENT	CAUSE OF DEATH/COMMENTS
108-6070305*	46/M	80	61	Found dead (in heat of 100°F). Autopsy report stated cause of death as acute and chromic asthmatic bronchitis and granulomatous myocarditis. ECG: Screening: QTc =366 msec Baseline: QTc =393 Week 6: QTc=395 Was on ziprasidone at time of death.
108-5920750*	39/F	120	8	Found dead one day after her estimated date of death of unknown cause. Subject's face was burned and it was thought that she had fallen against a hot water pipe. The investigator's postmortem diagnosis was alcohol abuse/diabetic ketoacidosis, but there is no evidence for this. No coroner's report located in the CRF. Was on ziprasidone at time of death.
116B-5080001*	54/M	120	71	Found dead in his hospital bed. Autopsy showed generalized atherosclerosis, coronary artery disease, cerebral artery disease, visceral congestion (liver, spleen, and lung), COPD, and cardiac hypertrophy. ECGs during the study: Screening: QTc=391 msec baseline: QTc=383 week 2: QTc=367 week 6:QTc=391 Subject had complaint of chest pain once during the study, but ECG was normal and diagnosed as anxiety. Was on ziprasidone at time of death.
302E-3190375*	48/M	120	162	Found dead. CRF showed hypertension and tachycardia on last day of study with hypertension as adverse event during study. Narrative states that subject had history of polydipsia and seizure disorder. Details regarding the death are unclear. Died one day after discontinuing ziprasidone.

Appendix Table 8.1.1.1 (con't)

304E-1930379**	52/M	80	221	Found dead while taking a nap. No autopsy performed and exact cause of death is unknown. ECG during the study as shown in the safety update: QTc at: Screening=374.7 msec Week 12=415.69 Week 28=413.12 with flat T wave in lead AVL; no evidence of ischemic changes. The CRF had minimal information and the patient profile in the safety update had different ECG QTc values than the original submission. Was on ziprasidone at time of death.
105-5340021*	70/F	2	5	Subject had sudden onset of shallow respirations and diaphoresis. Death certificate stated acute cardiopulmonary arrest due to arteriosclerotic cardiovascular disease. Subject with history of right bundle branch block, otherwise ECG was normal. Was taking ziprasidone just prior to death.
308-0350003*	63/M	80	485	Sudden collapse and died. Coroner's report stated that cause was a ruptured abdominal aortic aneurysm and atherosclerosis. Was on ziprasidone at the time of death.
115-6940394	43/M	40	16	Found dead. Coroner's cause of death listed as asphyxiation due to aspiration of vomit . Was on risperidone, clonazepam and lorazepam at time of death. Subject had difficulty breathing three days before death, and complained of dyspnea on morning of death. Died 29 days after discontinuing ziprasidone.
301-3110977	28/F	120	62	Died suddenly of unknown causes. Upon discontinuing ziprasidone, this cachetic subject complained of substernal pinching and ECG changes showed an arrhythmia with probable subendocardial ischemia. She was treated with thioridazine and nitrazepam, and died two days later. Autopsy reportedly showed evidence of myocardosis. Coroner's report not found in CRF. **Death occurred two days after stopping ziprasidone.**

Appendix Table 8.1.1.1 (con't)				
116B-6590001	44/F	120	47	Subject had a UTI upon d/c and was diaghosed with gastritis with Helicobacter pylori 13 days later. She was seen in ER with diagnosis of panic attack 21 days after d/c (three days prior to death). Sponsor reports that the autopsy was not available due to legal issues in medical examiners, but Subject's attending physician reportedly got information from the medical examiners that subject had a benign cardiac neoplasm (myxoma).ECG: screening: QTc=444 msec baseline: QTc=443 week 1: QTc=433 week 2: QTc=440 week 6: QTc=407 Subject reported chest pain one day after starting ziprasidone: cardiology w/u was normal, but had elevated transaminases. Episodes of tachycardia and hypertension during the study: day 6:102 bpm day 20:120/100; 104 bpm day 27:140/100; 102 bpm day 42:164/98 It is unclear what medications she was on as the patient summary and the CRF do not list the same medications. **Subject stopped ziprasidone 24 days before her death.**
303-1970299	79/F	80	30	Cardiac arrest. No autopsy was performed. Subject had new diagnosis of atrial fibrillation and ischemic heart disease 27 days after d/c. At time of death was taking perphenazine, deparkin, digoxin, verapamil, and enalapril. **Death occurred 30 days after d/c from ziprasidone.**
Suicides and accidents				
108-6090381	21/F	160	54	Suicide by gunshot while on ziprasidone.
116B-6940004	24/M	160	146	Suicide by hanging while on ziprasidone. Subject had been complaining of increasing depressed mood; treatment included an increase in ziprasidone.
117-6870317	51/M	120	205	Death by defenestration. According to study profile, subject did not appear suicidal prior to death.
117-7060529	40/M	160	54	Subject stopped ziprasidone on his own and four days later he drove his car off a cliff. Subject was driving his car after a sleep deprived EEG against medical advice. Autopsy listed asphyxiation due to drowning and was classified as a probable traffic accident.
302-2600156	46/M	120	7	Subject's body found drowned in local river after being missing from the hospital for five days.
302E-1590029	22/M	120	179	Suicide by falling under a train. Was being treated with ziprasidone at time of suicide with plans to be admitted to the hospital that same day.
JP-95-6011622[1♦]	53/M	53	20	Suicide seventeen days after discontinuing ziprasidone (Japanese studies: not part of the integrated safety data base.)

*Included in Sudden Unexpected Death (SUD) rate calculation in Appendices 8.1.1.3 and 8.1.1.4

[1] Submitted in the safety update

♦Not included in integrated safety data base

Appendix Table 8.1.1.1 (con't)

Ziprasidone subjects who died ≥ 30 days after treatment

SUBJECT #	AGE/ SEX	DOSE (MG/D)	DURATION (DAYS)	CAUSE OF DEATH
104-5130213	40/M	40	28	Sudden death; cause unknown. Occurred 7½ months after discontinuation from ziprasidone .
106-05550117	35/M	40	27	Unknown cause of death but possible seizure and aspiration of vomit. Was taking risperidone at time of death. Death occurred 4½ months after stopping ziprasidone .
108-5780020	37/M	80	8	Accidental drowning. Died 1½ months after stopping ziprasidone .
117-6940542	38/M	160	15	Suicide by gun shot one year after d/c from ziprasidone .
301-1140331	30/M	200	26	Died of complication due to pancreatitis 9 months after stopping ziprasidone
301-1320771	34/M	120	53	Suicide by hanging approximately 3 months after stopping ziprasidone .
303-0640276	61/M	40	69	Died of bronchopneumonia with bronchial adenocarcinoma and metastasis. Death occurred 4 months after stopping ziprasidone.
303-1950250	68/M	40	350	Died of cranial trauma 2° to fall. Ziprasidone was stopped 45 days prior to death.
303-1950281	71/F	40	61	Sudden death due to acute purulent leptomeningitis. Death occurred 4 ½ months after stopping ziprasidone.
303-1970269	67/F	80	37	Bronchopneumonia. Stopped ziprasidone112 days before diagnosis.
303-1990089 no CRF available	55/M	80	27	Sudden death due to acute cerebral edema. death occurred 60 days after stopping ziprasidone.
303-2120222 [1]	58/M	160	349	Died of post operative cerebral edema after tumor removal. Occurred two months after stopping ziprasidone
304-2040222	55/F	160	29	Sudden death with proposed cause of acute heart failure due to pulmonary disease. Death occurred approximately 2 months after stopping ziprasidone.
307-2690047** [1]	49/F	100	196	Died of hepatic coma, cholestatic jaundice and malignant neoplasm 95 days after stopping ziprasidone. Discontinued ziprasidone because of jaundice and elevated AST (244 U/L) and ALT (375 U/L).

**Died after cutoff of 5/15/97

[1]Submitted in the safety update

Appendix Table 8.1.1.1 (con't)

From the sponsor's electronic submission:

Deaths in Risperidone group (table from sponsor's electronic submission)

Treatment Group: Risperidone

Subject I.D.	Preferred text /Investigator text	Age at onset	Sex	Race	Weight (KG)	Duration of Treatment (Days)	Dose at onset (mg)	Mode Dose (mg)	Maximum Dose (mg)	Onset (Day)	Treatment discontinued	Serious adverse event type
117 06979223	FOREIGN BODY IN LARYNX / ASPHYXIATION DUE TO ASPIRATION OF FOOD	65	Male	Caucasian	93.4	201	4	4	6	201	No	DEATH / AELIFETH

Deaths in Haloperidol group (table from sponsor's electronic submission) :

Subject I.D.	Preferred text /Investigator text	Age at onset	Sex	Race	Weight (KG)	Duration of Treatment (Days)	Dose at onset (mg)	Mode Dose (mg)	Maximum Dose (mg)	Onset (Day)	Treatment discontinued	Serious adverse event type
168 06829040	SUICIDE/SELF-INFLICTED INJURY BY OTH/UNSP FIREARM / SELF INFLICTED GUNSHOT WOUND	23	Male	Caucasian	64.9	84	N/A			102	No	DEATH
168 06940564	POISONING BY UNSPECIFIED DRUG/MEDICINAL SUBSTANCE / INTENTIONAL DRUG OVERDOSE	30		Other			N/A				No	DEATH
	SUICIDE/SELF-INJURY BY UNSPECIFIED MEANS / SUICIDE	30		Other			N/A				No	DEATH
	SUICIDE/SELF-POISONING BY CORROSIVE/CAUSTIC SUBST / INTENTIONAL INGESTION OF CORROSIVE SUBSTANCE	30		Other			N/A				No	DEATH
168E06840077	ACUTE MI, UNSPECIFIED SITE, UNSPECIF EPISODE CARE / ACUTE MYOCARDIAL INFARCTION	72		Other			N/A				Yes	DEATH / AEHOSP

Deaths in Placebo Group (Table from the sponsor's electronic submission):

Treatment Group: Placebo

Subject I.D.	Preferred text /Investigator text	Age at onset	Sex	Race	Height (CS)	Duration of Treatment (Days)	Dose at onset (mg)	Mode Dose (mg)	Maximum Dose (mg)	Onset (Day)	Treatment discontinued	Serious adverse event type
106 06540018	CONGESTIVE HEART FAILURE / CONGESTIVE HEART FAILURE	82	Female	Caucasian	76.0	21	0	0	0	76	No	DEATH / AEHOSP
	RESPIRATORY FAILURE / RESPIRATORY FAILURE	82	Female	Caucasian	76.0	21	0	0	0	76	No	DEATH / AEHOSP
106 06540019	PNEUMONITIS DUE TO INHALATION OF FOOD OR VOMITUS / ASPIRATION PNEUMONIA	87	Female	Caucasian	46.0	13	0	0	0	17	Yes	DEATH / AELIFETH / AEHOSP
	RESPIRATORY FAILURE / RESPIRATORY FAILURE	87	Female	Caucasian	46.0	13	0	0	0	17	Yes	DEATH / AELIFETH / AEHOSP
106 06610063	PYREXIA OF UNKNOWN ORIGIN / COMPLICATIONS OF HYPERTHERMIA	34	Male	Caucasian	79.6	14	0	0	0	61	No	DEATH
106 06620126	POISONING BY ANTIALLERGIC AND ANTIEMETIC DRUGS / INTENTIONAL OVERDOSE - DIPHENHYDRAMINE	37	Female	Caucasian	79.4	32	0	0	0	39	No	DEATH
	SUICIDE/SELF-INJURY BY UNSPECIFIED MEANS / SUICIDE	37	Female	Caucasian	79.4	32	0	0	0	39	No	DEATH
303 01810067	MALIGNANT NEOPLASM OF PLEURA, UNSPECIFIED / LEFT SIDE PLEURAL MESOTHELIOMA	43	Male	Caucasian	86.0	232	0	0	0	286	Yes	DEATH / AELIFETH / AEHOSP
	SEC/UNSP MALIGN NEOPL LYMPH NOD(S)INTRATHORACIC / METASTASES TO MEDIASTINAL LYMPH NODES	43	Male	Caucasian	86.0	232	0	0	0	286	Yes	DEATH / AELIFETH / AEHOSP
	SECONDARY MALIGN NEOPL OF LIVER, SPEC AS SECONDARY / METASTASES TO LIVER	43	Male	Caucasian	86.0	232	0	0	0	286	Yes	DEATH / AELIFETH / AEHOSP
303 01970272	BRONCHOPNEUMONIA, ORGANISM UNSPECIFIED / BRONCHOPNEUMONIA	76	Male	Caucasian	66.0	16	0	0	0	19	No	DEATH
303 02120224	ACUTE PANCREATITIS / ACUTE HEMORRHAGIC PANCREATITIS	66	Female	Caucasian	70.0	10	0	0	0	49	No	DEATH
	PULMONARY EMBOLISM AND INFARCTION / PULMONARY EMBOLISM	66	Female	Caucasian	70.0	10	0	0	0	49	No	DEATH
	UNSPECIFIED CIRCULATORY SYSTEM DISORDER / CIRCULATORY INSUFFICIENCY	66	Female	Caucasian	70.0	10	0	0	0	49	No	DEATH
307 01780094	EXTRD HEMOR POST INJURY W/O OPEN IC WND, UNSP CONC / EXTRADURAL HEMATOMA	43					N/A				No	DEATH
307 02120122	HEART DISEASE, UNSPECIFIED / CARDIAC DECOMPENSATION	73					N/A				Yes	DEATH / AELIFETH / AEHOSP
	PNEUMONIA, ORGANISM UNSPECIFIED / LEFT SIDED PNEUMONIA	73					N/A				Yes	DEATH / AELIFETH / AEHOSP

APPENDIX 8.1.1.2 Mortality rate for Phase II/III clinical programs in ziprasidone NDA 20-825

DRUGS	Number of Subjects [1]	Subject-years exposure [1]	Total # deaths	# deaths ≤ 30 days	Crude mortality rate [2]	Mortality per 100 subject-years [2]
Ziprasidone	2588	772	31 [3]	17	0.007	2.20
Placebo	382	52	9	5	0.013	9.62
Haloperidol	585	131	3	3	0.005	2.29
Risperidone	295	105	1	1	0.003	0.95

[1]Includes integrated safety data base, Study 105 (IM: ziprasidone n=11; placebo n=12) and Study 120 (dementia: ziprasidone n=12)
[2]Based on # of deaths ≤ 30 days
[3]Does not include subject 307-269-0047 (died after the cut-off date of 5/15/97) and subject JP-95-6011622

APPENDIX 8.1.1.3 Rate of Sudden Unexpected Death* (SUD) in ziprasidone NDA 20-825

DRUGS	Number of Subjects [1]	Subject-years exposure	# Sudden Deaths	SUD per 1000 subject years
Ziprasidone	2588	772	7#	9.1
Placebo	382	52	0	0
Haloperidol	585	131	0	0
Risperidone	295	105	1	9.5

*Sudden Unexpected Death (SUD) refers to subjects found dead or who died within 24 hours of symptoms
Refer to Appendix 8.1.1.1 for listing of deaths considered to be SUD.
#Does not include subject 115-6940394; please refer to the text of Section 8.1.1
[1]Includes integrated safety data base, Study 105 (IM: ziprasidone n=11; placebo n=12) and Study 120 (dementia: ziprasidone n=12)

APPENDIX 8.1.1.4 Rate of SUD in most recently submitted antipsychotic NDA data bases *

DRUGS	Subject-years exposure	# Sudden Deaths	SUD per 1000 subject years
Ziprasidone	772	7	9.1
Sertindole	476	5	10.5
Olanzapine	1122.2	4	3.5
Risperidone	508	2	3.9
Quetiapine	865.3	1	1.1

*Sources are the current NDA 20-852 and Review of Clinical Data: *General Characteristics of the Deaths in the NDAs for Olanzapine, Risperidone, Quetiapine and Sertindole* by Greg Burkhart, M.D. (HFD-120: 3/3/98)

APPENDIX 8.1.2

SUMMARY OF NONFATAL SERIOUS ADVERSE EVENTS OCCURING IN SUBJECTS TAKING ZIPRASIDONE AND CONSIDERED UNLIKELY TO BE DRUG RELATED

Subject #	Age/Sex	Modal Dose (mg/d)	Duration (days)	Adverse Event
Cardiac				
101-5050003	33/M	40	28	Syncopal event. Ziprasidone was d/ced 11 days prior to episode and subject was on multiple medications at time of incident.
104-5220146	45/F	80	12	Subject hospitalized with hypertensive episode with diastolic pressure up to 120 mm Hg, tremouslousness and weakness. Subject with history of hypertension which had been stable with nifedipine.
106-5520124	41/M	40	15	Hypertension with peak of 152/110. No h/o of hypertension also had facial rash (see dermatology)
116B-5510007	44/M	120	12	Chest pain, thought to be anxiety. Subject was hospitalized for observation and sponsor concluded this was a manifestation of anxiety.
116B-6590008	72/F	80	239	Hypertension of 200/90. Profile states that subject had a history of hypertension, but it was normal for the six months of the study prior to this onset.
118-7090004	40/M	40	4	Sinus bradycardia (48 bpm) at end of study. Elevated CPK, but this was not checked until the end of the study just as subject started risperidone.
303-2120105	56/M	160	280	Hypertensive episode (220/140) fell down steps resulting in subdural hematoma, skull fracture, pneumothorax
Gastrointestinal				
106-5550119	57/F	120	7	Incarcerated left inguinal hernia
109-5720027	49/F	80	3	Subject was hospitalized for chest pain; original work-up in CRF suggested ECG changes of QTc prolongation. Cardiology work up was negative and Dr. Charles Ganley, HFD-110 consultant, determined that ECGs did not reflect true QTc changes. Final diagnosis was exacerbation of gastroesophageal reflux.
116B-6590001	44/F	120	47	Gastritis with Helicobacter pylori diagnosed 13 days after discontinuing ziprasidone. Died of benign cardiac neoplasm (myxoma) 24 days after stopping ziprasidone.
303-2710228	54/M	160	87	Subject had heartburn, epigastric pain and weight loss and within three weeks of these symptoms discontinued ziprasidone and was hospitalized. Endoscopy showed chronic gastritis with Helicobacter pylori.

APPENDIX 8.1.2 (CON'T)				
Genitourinary				
116B-5870006	37/F	160	256	Hysterectomy and B/L oophorectomy
116B-5900005	33/F	160	440	Uterine Fibroids
117-6220029	53/M	40	4	benign prostatic hypertrophy
117-6380304	57/F	80	363	Total abdominal hysterectomy
117-6690008	39/F	160	315	Urinary bladder suspension surgery.
Pulmonary				
105-5340006	86/F	6	57	Tracheobronchitis 2⅓ months after d/c of ziprasidone
106-5550136	59/M	40	2	Asthma attack; subject with history of COPD.
106E-5550133	60/F	40	92	chest pain/exacerbation of COPD/bronchitis/adenovirus
110-5370007	33/M	60	4	Diagnosed with lung cancer five days after d/c of ziprasidone
116B-5680007	43/F	120	240	Test positive for HIV virus and had event of pneumocystis crainii
116B0-74004/ 108-5740080	33/M	80	301	Spontaneous pneumothorax
Metabolic				
117-5130512	35/M	120	194	Diabetic episode with 16 lb. wt loss and thirst and ketoacidosis
116B-6940003	26/M	200	164	Nausea, vomiting and loss of appetite. Weight loss of > 30 lb; was hospitalized for exacerbation of schizophrenia. . Also, loss of appetite, n/v.
117-5080350	75/M	80	52	Dehydration, erratic eating pattern associated with exacerbation of schizophrenia in this subject. Weight loss of 13.5 lb.
Miscellaneous				
101-05060084	52/M	4	20	Hyponatremia (Na=111), confusion. Hospitalized, resolved in 2 days with fluid restriction. Ziprasidone was discontinued.
104-05250132	64/M	40	28	Cellulitis, right lower leg occurring twenty-two days after d/c of ziprasidone.
104-5200275	63/F	80	28	Fall (unclear how subject fell) with fracture of left humeral head on day 15; on day 24, subject developed right lower leg cellulitis and lymphangitis and was treated with antibiotics, bedrest, and leg soaks.
116B-665008/ 117-6650101	23/M	160	365	Knee surgery.
118-709-0004	40/M	20	4	Pt had elevated CPK, but no CPK levels done until the subject was taking risperidone 1 day after taking ziprasidone. At that time the CPK levels were very high (702 U/L) and were eventually stabilized and decreased to 544 U/L before subject was discharged from the hospital.

APPENDIX 8.1.2 (CON'T)				
303-01980076	44/M	80	364	Subject was mugged and had brain concussion and facial contusions.
303-2640336	34/M	160	359	2nd degree burns of face, neck and shoulder from fire at psychiatry clinic.
303-2120222	58/M	160	349	Blood pressure was 180/90 after this loss of consciousness (2-3minutes). No ECG changes, but CT showed cerebral neoplasm.
*From Japanese study which is not part of integrated safety data base	51/F	40,80 or 100 mg/d	24	Hyponatremia (Na=110 MEq/L), hypokalemia (K=3.2Meq/L),CPK=10,760 U/L, ↑ AST=91, ↑cortisol (32 ug/ml), LDH=796 U/L, 3+ blood in urine and decreased level of consciousness (unresponsive to verbal stimulation and abnormal reflexes). Hypertension (208/110) and tachycardia (110/min)Baseline values were normal for the above tests except for K=5.3 Meq/L. Within 8 days of hospitalization, this subjects level of consciousness improved and she was able to eat without assistance. This incident occurred 8 days after discontinuation of ziprasidone (she had akathisia and worsening depression) and subject was taking biperidene and sulpiride at time of the incident.
Overdose				
114-7150457	20/M	160	20	Overdose of metformin.
116B-5510005	38/M	80	72	Overdosed with acetylsalicylic acid.
116B-5950018	33/F	200	182	Overdosed on lorazepam and flurazepam in presence of hospital staff.
116B-6020005	27/M	160	159	Overdosed on lorazepam 10 days after d/c of ziprasidone.
117-05080352	54/M	80	308	Subject overdosed on chloral hydrate and lorazepam was treated with activated charcoal and developed rhabdomyolysis with nerve damage in leg. This occurred one day after d/c of ziprasidone.
117-06310477	35/F	80	92	Overdose on lithium eight days after d/c of ziprasidone.

Note: Psychiatric serious adverse events are not discussed in this review, as it is not always possible to distinguish between the effects of the study drug and the symptoms of the underlying illness.

Appendix 8.1.5.3 (From Sponsor's Electronic Submission)

Treatment-Emergent Adverse Events Reported in at Least 1% of Ziprasidone Subjects (All Causalities)
Incidence Rate for Ziprasidone Greater than Placebo
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies

	Ziprasidone	Haloperidol	Placebo
Number of Subjects: Evaluable for Adverse Events	702	85	273
% With Adverse Events			
BODY AS A WHOLE			
ACCIDENTAL INJURY	4.0	2.4	1.5
ASTHENIA	4.6	8.2	2.6
CHEST PAIN	3.3	2.4	2.9
INFECTION	1.3		0.7
CARDIOVASCULAR			
POSTURAL HYPOTENSION	1.3	2.4	0.4
TACHYCARDIA	1.6	2.4	1.1
DIGESTIVE			
ANOREXIA	1.9	4.7	1.1
CONSTIPATION	9.3	7.1	8.4
DIARRHEA	4.8	4.7	4.4
DRY MOUTH	4.1	11.8	2.2
DYSPEPSIA	8.1	15.3	7.0
INCREASED SALIVATION	1.3	1.2	0.7
NAUSEA	9.5	9.4	7.0
MUSCULOSKELETAL			
ARTHRALGIA	3.3	2.4	2.9
MYALGIA	1.1		0.4
NERVOUS			
AKATHISIA	8.4	28.2	7.0
ANXIETY	4.4	1.2	4.0
DIZZINESS	7.8	9.4	6.9
DYSTONIA	4.0	11.8	2.2
EXTRAPYRAMIDAL SYNDROME	4.7	14.1	1.1
HYPERTONIA	3.4	11.8	1.8
SOMNOLENCE	14.4	23.5	6.6
TREMOR	2.4	10.6	1.8
RESPIRATORY			
COUGH INCREASED	2.6	2.4	0.7
RESPIRATORY DISORDER	4.8		1.1
RESPIRATORY TRACT INFECTION	3.0	8.2	2.2
RHINITIS	3.7		2.2
SKIN AND APPENDAGES			
FUNGAL DERMATITIS	1.7		1.1
RASH	4.1	2.4	3.3
SPECIAL SENSES			
ABNORMAL VISION	2.7	4.7	1.5
CONJUNCTIVITIS	1.1	1.2	1.1
UROGENITAL			
URINARY INCONTINENCE	1.3	1.2	1.1

Subjects with multiple occurrences of the same adverse event are counted only once for that adverse event.
Only adverse events occurring while on study treatment or within the six days after the last day of study treatment were included in this table.
Protocols: 104,106,114,115

Appendix 8.1.5.4
(Selected from Sponsor's Proposed Labeling)

Other Adverse Events Observed During the Premarketing Evaluation of Ziprasidone - Following is a list of COSTART terms that reflect treatment- emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with ziprasidone at multiple doses > 4 mg/ day within the database of 2163 patients. All reported treatment- related events are included except those already listed in Table 1 or elsewhere in labeling, those event terms which were so general as to be uninformative, and events reported only once and which did not have a substantial probability of being acutely life- threatening. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/ 100 patients (only those not already listed in the tabulated results from placebo- controlled trials appear in this listing); infrequent adverse events are those occurring in 1/ 100 to 1/ 1000 patients; rare events are those occurring in fewer than 1/ 1000 patients.

Body as a Whole *Frequent:* abdominal pain, back pain, fever, flu syndrome, headache, pain, suicidal ideation: *Infrequent:* , abscess, accidental fall, accidental overdose, allergic reaction, cellulitis, chills, bacterial infection, fungal infection, intentional overdose, lab test abnormal, malaise, photosensitivity reaction, suicide attempt: *Rare:* abdomen enlarged, hangover effect, neoplasm, pelvic pain.

Cardiovascular System *Frequent:* hypertension, hypotension: *Infrequent:* angina pectoris, arrhythmia, bradycardia, electrocardiogram abnormal, hemorrhage, migraine, palpitation, syncope, vasodilation. *Rare:* peripheral vascular disorder, QT interval prolonged, retinal vascular disorder.

Digestive System *Frequent:* vomiting: *Infrequent:* cheilitis, duodenal ulcer, dysphagia, flatulence, gastritis, gastroenteritis, gingivitis, increased appetite, liver function tests abnormal,

oral moniliasis, rectal hemorrhage, tongue edema, tooth caries: *Rare:* eructation, fecal incontinence, gum hemorrhage, stomach ulcer.

Hemic and Lymphatic System *Infrequent:* anemia, ecchymosis, eosinophilia, leukocytosis, leukopenia: *Rare:* iron deficiency anemia, thrombocytopenia.

Metabolic and Nutritional Disorders *Frequent:* weight gain, weight loss: *Infrequent:* albuminuria, dehydration, edema, hyperglycemia, peripheral edema, SGOT increased, SGPT increased, thirst: *Rare:* bilirubinemia, hypercholesteremia.

Musculoskeletal System *Infrequent:* arthrosis, bone pain, leg cramps, myasthenia, tenosynovitis.

Nervous System *Frequent:* agitation, delusions, depression, dyskinesia, hallucinations, hostility, insomnia, manic reaction, myoclonus, nervousness, paranoid reaction, paresthesia, personality disorder, psychosis, schizophrenic reaction, speech disorder, tardive dyskinesia, thinking abnormal, twitching: *Infrequent:* abnormal dreams, abnormal gait, akinesia, amnesia, apathy, ataxia, catatonic reaction, choreoathetosis, cogwheel rigidity, confusion, convulsion, delirium, dementia, depersonalization, drug dependence, dysarthria, emotional lability, euphoria, grand mal convulsion, hyperkinesia, hypesthesia, hypokinesia, libido decreased, libido increased, neurosis, oculogyric crisis, paralysis, sleep disorder, stupor, vertigo,

withdrawal syndrome: *Rare:* diplopia, incoordination, neuropathy, nystagmus.

Respiratory System *Frequent:* bronchitis, dyspnea, pharyngitis: *Infrequent:* asthma, epistaxis, pneumonia, respiratory distress syndrome, sinusitis: *Rare:* pneumothorax, voice alteration.

Skin and Appendages *Frequent:* pruritus: *Infrequent:* acne, alopecia, contact dermatitis, dry skin, eczema, exfoliative dermatitis, herpes simplex, maculopapular rash, psoriasis, seborrhea, skin hypertrophy, skin ulcer, sweating, urticaria, vesiculobullous rash: *Rare:* furunculosis, lichenoid dermatitis, pustular rash.

Special Senses *Infrequent:* blepharitis, deafness, dry eyes, ear pain, eye pain, otitis externa, otitis media, retinal disorder, taste perversion, tinnitus: *Rare:* abnormality of accommodation, mydriasis.

Urogenital System *Infrequent:* abnormal ejaculation, amenorrhea, cystitis, dysmenorrhea, dysuria, gynecomastia, hematuria, impotence, leukorrhea, menorrhagia, metrorrhagia, polyuria, urinary frequency, urinary retention, vaginitis: *Rare:* anorgasmia, breast pain, kidney pain, nephritis, pyelonephritis, uterine fibroids enlarged.

Appendix 8.1.6.3.1 Mean Change from Baseline to Last Observation for Laboratory Test Data
Short-term Fixed-Dose Placebo Controlled from Phase II/III*
(adapted from sponsor's electronic submission)

			Ziprasidone			Placebo		
GROUP	PARAMETER	UNITS@	N	BASELINE MEDIAN	CHANGE FROM BASELINE	N	BASELINE MEDIAN	CHANGE FROM BASELINE
HEMATOLOGY	Hemoglobin (HGB)	G/DL	680	15.3	-0.1	261	15.1	0.1
	Hematocrit (HCT)	%	679	45	-1	261	46	0
	RBC Count	MILL/CMM	680	4.9	0	261	4.9	0
	Platelets	THOU/CMM	678	266	0	260	256	-1
	WBC Count	THOU/CMM	680	7.4	0.1	261	7.5	0
	Eosinophils (%)	%	679	3	0	261	3	0
	Neutrophils (abs)	THOU/CMM	679	4.41	0.13	261	4.94	-0.06
LIVER FUNCTION	Total Bilirubin	MG/DL	681	0.6	0	261	0.6	0.1
	Total Protein	G/DL	682	7.1	0	261	7.2	0
	Serum Albumin	G/DL	681	4.3	0	261	4.3	0
	Serum Globulin	G/DL	680	2.9	0	260	3	0
	SGOT(AST)	IU/L	682	18	0	261	18	0
	SGPT(ALT)	IU/L	681	20	0	261	19	-1
	LDH	IU/L	682	140	4	261	142	1
	Alk. Phosphatase	IU/L	682	73	-1	261	76	-1
RENAL FUNCTION	Blood Urea Nitrogen	MG/DL	682	13	-1	261	12	0
	Serum Creatinine	MG/DL	682	1	0	261	1	0
ELECTROLYTES	Uric Acid	MG/DL	682	5.2	0.2	261	5.2	0.2
	Sodium	MEQ/L	682	140	0	261	140	0
	Potassium	MEQ/L	682	4.4	0	261	4.4	0
	Chloride	MEQ/L	682	103	0	261	103	1
	Bicarbonate	MEQ/L	2	22	1	.	.	.
	Calcium	MG/DL	682	9.6	0	261	9.6	0
	Phosphorus	MG/DL	681	3.8	0	261	3.8	-0.1
	Glucose, Fasting	MG/DL	3	86	2	1	190	-41
	Glucose, Random	MG/DL	678	93	0	259	93	3
	Magnesium	MG/DL	1	2	0	.	.	.
LIPIDS	Cholesterol	MG/DL	682	185	-3	261	186	-2
	Triglycerides	MG/DL	681	126	-6	260	130	-13
URINE	Specific Gravity		679	1.02	0	258	1.02	0
	Urine pH		678	6.5	0	258	6.5	0
	Protein (qual)		588	0	0	214	0	0
	Urine Glucose		588	0	0	214	0	0
	Ketones (qual)		588	0	0	214	0	0
	Bilirubin (qual)		588	0	0	214	0	0

Based on Laboratory Test Results.
1. Converted to Standard Reporting Units
2. Adjusted to a Common Set Upper and Lower Reference Limits
@ Kruskal-Wallis test yielded a significant association at the .05 level of alpha by using the RANK and ANOVA procedures

*The sponsor clarified that these were studies 104, 106, 114, 115

Appendix 8.1.6.3.2a Sponsor's Laboratory Reference Ranges to Determine Baseline Abnormality (11/7/97 submission from sponsor)

Ziprasidone Project Laboratory Reference Ranges

TEST	REF_MIN	REF_MAX	STDUNIT
Hemoglobin			G/DL
Hematocrit			%
Red Blood Cells			MILL/CMM
Platelets			THOU/CMM
White Blood Cells			THOU/CMM
Eosinophils (%)			%
Erythrocyte Sedimentation Rate			MM/H
Prothrombin Time Quick			SEC
Total Bilirubin			MG/DL
Direct Bilirubin			MG/DL
Protein (total)			G/DL
Albumin			G/DL
Globulin			G/DL
Aspartate Aminotransferase (GOT)			IU/L
Alanine Aminotransferase (GPT)			IU/L
Lactate Dehydrogenase			IU/L
Alkaline Phosphatase			IU/L
Blood Urea Nitrogen			MG/DL
Creatinine			MG/DL
Urate			MG/DL
Sodium			MEQ/L
Potassium			MEQ/L
Chloride			MEQ/L
Bicarbonate			MEQ/L
Calcium			MG/DL
Phosphate			MG/DL
Cholesterol			MG/DL
Triglycerides			MG/DL
Glucose (fasting)			MG/DL
Glucose (random)			MG/DL
Urine Specific Gravity			
Urine pH			
Urine Protein			
Urine Glucose			
Urine WBC			/HPF
Urine RBC			/HPF
Urine Ketones			
Urine Granular Casts			/LPF
Urine Hyaline Casts			/LPF
Urine Bilirubin			

Appendix 8.1.6.3.2a (con't) Sponsor's Laboratory Reference Ranges to Determine Baseline Abnormality (11/7/97 submission from sponsor)

Cholesterol (LDL)	MG/DL
Cholesterol (HDL)	MG/DL
Thyroxine (T4)	MCG/DL
Magnesium	MG/DL
Prolactin	NG/ML
Urine Calcium	MG/DAY
Urine Glucose (24 Hr) Quantitative	MG/DAY
Urine (24hr) Protein	MG/DAY
TSH	MCIU/ML
Urine WBC Cast	/LPF
Urine (24hr) Creatinine	MG/DAY
Urine RBC Casts	/LPF
Neutrophils (Abs)	THOU/CMM

Appendix 8.1.6.3.2b Sponsor's criterion for determining post baseline clinical significance of laboratory values (adapted from sponsor's submission of 11/7/97)

					Column "A"	Column "B"
Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnormal (Tier 2)
1	Hemoglobin (HGB)	G/DL	HEMATOLOGY	> 1.0 x ULN	>20% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>20% Decrease from baseline	< 90% of baseline
2	Hematocrit (HCT)	%	HEMATOLOGY	> 1.0 x ULN	>20% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>20% Decrease from baseline	< 90% of baseline
3	RBC Count	MILL/CMM	HEMATOLOGY	> 1.0 x ULN	>25% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>25% Decrease from baseline	< 90% of baseline
5	Platelets	THOU/CMM	HEMATOLOGY	> 1.0 x ULN	> 700	> 120% of baseline
				< 1.0 x LLN	< 75	< 80% of baseline
7	WBC Count	THOU/CMM	HEMATOLOGY	> 1.0 x ULN	> 17.5	> 125% of baseline
				< 1.0 x LLN	< 2.5	< 75% of baseline
14	ESR	MM/H	HEMATOLOGY	> 1.0 x ULN (x)	> 1.2 x ULN	> 120% of baseline
19	Prothrombin Time	SEC	HEMATOLOGY	> 1.0 x ULN	> 1.2 x ULN	> 120% of baseline
608	Neutrophils (abs)	THOU/CMM	HEMATOLOGY	< 1.0 x ULN	<1.0	< 75% of baseline
9	Eosinophils (%)	%	HEMATOLOGY	> 1.0 x ULN	>= 10%	> 150% of baseline
21	Total Bilirubin	MG/DL	LIVER FUNCTION	> 1.0 x ULN (x)	> 1.5 x ULN	> 150% of baseline
22	Direct Bilirubin	MG/DL	LIVER FUNCTION	> 1.0 x ULN (x)	> 1.5 x ULN	> 150% of baseline
24	Total Protein	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	0.9 < x LLN	< 90% of baseline
25	Serum Albumin	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.1 x ULN	> 120% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 80% of baseline
26	Serum Globulin	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.2 x ULN	> 150% of baseline
				< 1.0 x LLN	< 0.8 x LLN	< 50% of baseline

Appendix 8.1.6.3.2b (con't) Sponsor's criterion for determining post baseline clinical significance of laboratory values (adapted from sponsor's submission of 11/7/97)

					Column "A"	Column "B"
Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnorma (Tier 2)
28	SGOT(AST)	IU/L	LIVER FUNCTION	>1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
30	SGPT(ALT)	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
32	LDH	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
35	Alkaline Phosphatase	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 150% of baseline
47	BUN	MG/DL	RENAL FUNCTION	> 1.0 x ULN (x)	> 1.3 x ULN	> 130% of baseline
48	Creatinine	MG/DL	RENAL FUNCTION	> 1.0 x ULN (x)	> 1.3 x ULN	> 130% of baseline
54	Sodium	MEQ/L	ELECTROLYTES	> 1.0 x ULN	> 1.05 x ULN	> 105% of baseline
				< 1.0 x LLN	< 0.95 x LLN	< 95% of baseline
55	Potassium	MEQ/L	ELECTROLYTES	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 90% of baseline
56	Chloride	MEQ/L	ELECTROLYTES	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 90% of baseline
57	Bicarbonate	MEQ/L	ELECTROLYTES	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 90% of baseline
58	Calcium	MG/DL	ELECTROLYTES	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 90% of baseline
59	Phosphorus	MG/DL	ELECTROLYTES	> 1.0 x ULN	> 1.2 x ULN	> 120% of baseline
				< 1.0 x LLN	< 0.8 x LLN	< 80% of baseline
50	Uric Acid	MG/DL	ELECTROLYTES	> 1.0 x ULN	> 1.2 x ULN	> 120% of baseline
199	Magnesium	MEQ/L	ELECTROLYTES	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 90% of baseline
63	Cholesterol	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 150% of baseline
173	HDL Cholesterol	MG/DL	LIPIDS	< 1.0 x LLN (?)	< 0.8 x LLN	< 80% of baseline
172	LDL Cholesterol	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 120% of baseline
64	Triglycerides	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 150% of baseline
67	Glucose, Fasting	MG/DL		> 1.0 x ULN	> 1.2 x ULN	> 150% of baseline
				< 1.0 x LLN	< 0.6 x LLN	< 50% of baseline
223	Prolactin	NG/ML		> 1.0 x ULN (x)	> 1.1 x ULN	> 150% of baseline

Appendix 8.1.6.3.2b (con't) Sponsor's criterion for determining post baseline clinical significance of laboratory values (adapted from sponsor's submission of 11/7/97)

					Column "A"	Column "B"
Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnormal (Tier 2)
78	Protein (qual)		URINE	> 1.0 x ULN	>= 2+	> baseline + 2
79	Urine Glucose		URINE	> 1.0 x ULN	>= 2+	> baseline + 2
80	Urine WBC	/HPF	URINE	> 1.0 x ULN	>= 6	> baseline + 6
81	Urine RBC	/HPF	URINE	> 1.0 x ULN	>= 6	> baseline + 6
86	Ketones (qual)		URINE	> 1.0 x ULN	>= 1+	> baseline + 1
88	Granular Casts	/LPF	URINE	> 1.0 x ULN	> 1	> baseline + 1
90	Hyaline Casts	/LPF	URINE	> 1.0 x ULN	> 1	> baseline + 1
115	Bilirubin (qual)		URINE	> 1.0 x ULN	>= 1+	> baseline + 1
600	Red Cell Cast	/LPF	URINE	> 1.0 x ULN	>= 1	> baseline + 1
442	White Cell Cast	/LPF	URINE	> 1.0 x ULN	>= 1	> baseline + 1
76	Specific Gravity		URINE	> 1.0 x ULN	> 1.035	> 1.035
				< 1.0 x LLN	< 1.000	< 1.000
77	Urine pH		URINE	> 1.0 x ULN	> 1.1 x ULN	> 1.1 x ULN
				< 1.0 x LLN	< 0.9 x LLN	< 0.9 x LLN
495	Creatinine	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
302	Calcium (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
308	Protein (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
307	Glucose (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline

Appendix 8.1.6.3.2c Incidence of Clinically Significant Laboratory Abnormalities for Short term Fixed-dose placebo controlled studies 104, 106, 114, 115. (adapted from sponsor's electronic submission)

Number of Subjects:	Ziprasidone	Placebo
Evaluable for laboratory abnormalities	688	261
With Clinically significant laboratory abnormalities	256 (37%)	86 (33%)

					Subjects with Abnormalities			Subjects with Abnormalities		
Group	Parameter	Units	Criteria*	@	N	n	%	N	n	%
HEMATOLOGY	Hemoglobin (HGB)	G/DL	> 20% decrease*		684	3	0	261	0	0
	Hematocrit (HCT)	%	> 20% decrease*		684	1	0	261	0	0
	RBC Count	MILL/CMM	> 25% decrease*		684	2	0	261	0	0
	Platelets	THOU/CMM	< 75		683	2	0	261	2	1
			> 700		683	0	0	261	0	0
	WBC Count	THOU/CMM	< 2.5		684	0	0	261	0	0
			> 17.5		684	4	1	261	1	0
	Eosinophils (%)	%	>= 10%		683	21	3	261	3	1
	Prothrombin Time	SEC	> 1.2 x ULN		2	0	0	1	0	0
	Neutrophils (abs)	THOU/CMM	< 1.0		683	3	0	261	1	0
	ESR	MM/H	> 1.2 x ULN					1	0	0
LIVER FUNCTION	Total Bilirubin	MG/DL	> 1.5 x ULN		685	2	0	261	0	0
	Direct Bilirubin	MG/DL	> 1.5 x ULN		9	1	11	4	0	0
	Total Protein	G/DL	< 0.9 x LLN		685	0	0	261	0	0
			> 1.1 x ULN		685	1	0	261	0	0
	Serum Albumin	G/DL	< 0.9 x LLN		685	0	0	261	0	0
			> 1.1 x ULN		685	0	0	261	0	0
	Serum Globulin	G/DL	> 1.2 x ULN		684	0	0	261	0	0
			< 0.8 x LLN		684	2	0	261	0	0
	SGOT(AST)	IU/L	> 3.0 x ULN		685	2	0	261	0	0
	SGPT(ALT)	IU/L	> 3.0 x ULN		684	8	1	261	1	0
	LDH	IU/L	> 3.0 x ULN		685	1	0	261	0	0
	Alk. Phosphatase	IU/L	> 3.0 x ULN		685	0	0	261	0	0
RENAL FUNCTION	Blood Urea Nitrogen	MG/DL	> 1.3 x ULN		685	1	0	261	0	0
	Serum Creatinine	MG/DL	> 1.3 x ULN		685	1	0	261	0	0
ELECTROLYTES	Uric Acid	MG/DL	> 1.2 x ULN		685	3	0	261	1	0
	Sodium	MEQ/L	< 0.95 x LLN		685	4	1	261	0	0
			> 1.05 x ULN		685	0	0	261	0	0
	Potassium	MEQ/L	< 0.9 x LLN		685	0	0	261	0	0
			> 1.1 x ULN		685	10	1	261	5	2
	Chloride	MEQ/L	< 0.9 x LLN		685	2	0	261	0	0
			> 1.1 x ULN		685	1	0	261	0	0
	Bicarbonate	MEQ/L	< 0.9 x LLN		21	0	0	6	0	0
			> 1.1 x ULN		21	0	0	6	0	0
	Calcium	MG/DL	< 0.9 x LLN		685	1	0	261	0	0
			> 1.1 x ULN		685	0	0	261	2	1
	Phosphorus	MG/DL	> 1.2 x ULN		685	7	1	261	6	2
			< 0.8 x LLN		685	2	0	261	0	0
ELECTROLYTES	Glucose, Fasting	MG/DL	> 1.2 x ULN		14	0	0	3	0	0
			< 0.6 x LLN		14	0	0	3	0	0
	Glucose, Random	MG/DL	> 1.2 x ULN		684	67	8	261	20	8
			< 0.6 x LLN		684	3	0	261	0	0
	Magnesium	MG/DL	< 0.9 x LLN		4	0	0	1	0	0
			> 1.1 x ULN		4	0	0	1	1	100
LIPIDS	Cholesterol	MG/DL	> 1.2 x ULN	@	685	16	2	261	0	0
	Triglycerides	MG/DL	> 1.2 x ULN	@	684	85	12	261	17	7
URINE	Specific Gravity		< 1.000		685	0	0	259	0	0
			> 1.035	@	685	0	0	259	4	2
	Urine pH		< 0.9 x LLN		685	0	0	259	0	0
			> 1.1 x ULN		685	3	0	259	3	1
	Protein (qual)		>= 2+		685	3	0	259	1	0
	Urine Glucose		>= 2+		685	2	0	259	0	0
	Urine WBC	/HPF	>= 6		666	63	11	228	21	9
	Urine RBC	/HPF	>= 6		661	32	6	223	21	9
	Ketones (qual)		>= 1+		685	11	2	259	4	2
	Granular Casts	/LPF	> 1		2	0	0	3	0	0
	Hyaline Casts	/LPF	> 1		5	3	60	4	1	25
	Bilirubin (qual)		>= 1+		684	1	0	259	0	0
	LDL Cholesterol	MG/DL	> 1.2 x ULN		1	0	0			
	HDL Cholesterol	MG/DL	< 0.8 x LLN		2	0	0			
	Protein (quant)	MG/DAY	> 1.1 x ULN		1	0	0	1	0	0
	White Cell Cast	/LPF	>= 1		1	1	100			
	Red Cell Cast	/LPF	>= 1		1	1	100			
HORMONES	Prolactin	NG/ML	> 1.1 x ULN		2	1	50			

Includes protocols 104, 106, 114, 115

N = Total number of subjects with at least one observation of the given lab parameter while on study treatment or during lag time.
n = Number of subjects with a clinically significant abnormality
* Change from baseline
@ Fisher Exact 2-tailed test yielded a significant association at the .05 level of alpha

Note: The criteria in this table lists only Column "A" from Appendix 8.1.6.3.2a when in fact both Column "A" and Column "B" were used to establish criteria for abnormal values in this table.

Appendix 8.1.6.4 Incident of Clinically Significant Laboratory Test in all oral Phase II/II Studie (adapted from sponsor's electronic submission)

Number of Subjects:	Ziprasidone	Placebo
Evaluable for laboratory abnormalities	1794	835
With clinically significant laboratory abnc	916 (51%)	157 (47%)

Group	Parameter	Units		Ziprasidone Subjects with Abnormalities N	n	%	Placebo Subjects with Abnormalities N	n	%
HEMATOLOGY	Hemoglobin (HGB)	G/DL		1778	6	0	833	1	0
	Hematocrit (HCT)	%		1778	2	0	833	1	0
	RBC Count	MILL/CMM		1778	4	0	833	0	0
	Platelets	THOU/CMM		1777	6	0	833	8	1
				1777	2	0	833	0	0
	WBC Count	THOU/CMM		1777	6	0	833	0	0
				1777	16	1	833	1	0
	Eosinophils (%)	%		1775	65	4	833	8	2
	ESR	MM/H		8	0	0	1	0	0
	Prothrombin Time	SEC		6	0	0	1	0	0
	Neutrophils (abs)	THOU/CMM		1771	9	1	833	1	0
LIVER FUNCTION	Total Bilirubin	MG/DL		1780	9	1	336	3	1
	Direct Bilirubin	MG/DL		19	1	5	5	0	0
	Total Protein	G/DL		1778	3	0	334	1	0
				1778	6	0	834	0	0
	Serum Albumin	G/DL		1780	3	0	334	1	0
				1780	1	0	334	0	0
	Serum Globulin	G/DL		1352	2	0	264	0	0
				1352	6	0	264	0	0
	SGOT (AST)	IU/L		1780	6	0	334	2	1
	SGPT (ALT)	IU/L		1776	17	1	334	2	1
	LDH	IU/L		1361	1	0	264	0	0
	Alk. Phosphatase	IU/L		1781	0	0	334	0	0
RENAL FUNCTION	Blood Urea Nitrogen	MG/DL		1363	3	0	264	1	0
	Serum Creatinine	MG/DL		1783	4	0	334	1	0
ELECTROLYTES	Uric Acid	MG/DL		1359	9	1	264	3	1
	Sodium	MEQ/L		1782	26	1	334	2	1
				1782	3	0	334	0	0
	Potassium	MEQ/L		1779	0	0	334	0	0
				1779	17	1	334	7	2
	Chloride	MEQ/L		1363	4	0	264	0	0
				1363	1	0	264	0	0
	Bicarbonate	MEQ/L		41	0	0	6	0	0
				41	0	0	6	0	0
	Calcium	MG/DL		1362	2	0	264	1	0
				1362	1	0	264	2	1
	Phosphorus	MG/DL		1361	16	1	264	7	3
ELECTROLYTES	Phosphorus	MG/DL		1361	8	1	264	1	0
	Glucose, Fasting	MG/DL		70	5	7	3	1	33
				70	0	0	3	0	0
	Glucose, Random	MG/DL		1344	178	13	264	32	12
				1344	7	1	264	0	0
	Magnesium	MG/DL		10	0	0	1	0	0
				10	0	0	1	1	100
LIPIDS	Cholesterol	MG/DL		1363	227	17	264	40	15
	Triglycerides	MG/DL		1359	322	24	264	48	18
URINE	Specific Gravity			1359	0	0	262	0	0
			#	1359	4	0	262	4	2
	Urine pH			1359	0	0	262	0	0
				1359	7	1	262	3	1
	Protein (qual)			1761	29	2	332	5	2
	Urine Glucose			1760	13	1	832	0	0
	Urine WBC	/HPF		1201	147	12	231	24	10
	Urine RBC	/HPF		1189	91	8	226	25	11
	Ketones (qual)			1760	41	2	332	11	3
	Granular Casts	/LPF		5	1	20	3	0	0
	Hyaline Casts	/LPF		17	9	53	4	1	25
	Bilirubin (qual)			1259	2	0	262	0	0
	LDL Cholesterol	MG/DL		4	0	0			
	HDL Cholesterol	MG/DL		6	0	0			
	Protein (quant)	MG/DAY		2	0	0	1	0	0
	White Cell Cast	/LPF		1	1	100			
	Urine Creatinine	MG/DAY		1	1	100			
	Red Cell Cast	/LPF		1	1	100			
HORMONES	Thyroxine (T4)	MCG/DL		218	4	2	57	1	2
				218	0	0	57	0	0
	Prolactin	NG/ML	#	741	148	20	75	3	4
	TSH	MCIU/ML		224	4	2	56	0	0
				224	8	4	56	1	2

Includes protocols 015, 101, 102, 104, 104e, 106, 106e, 108, 108e, 109, 109e, 110, 111, 114, 115, 116B, 117, 118, 122, 301, 302, 303, 304, 305

N = Total number of subjects with at least one observation of the given lab parameter while on study treatment or during lag time.
n = Number of subjects with a clinically significant abnormality
* Change from baseline
# Fisher Exact 2-tailed test yielded a significant association at the .05 level of alpha
Criteria for clinically significant laboratory abnormalities not adjusted for abnormal baseline laboratory values

Appendix 8.1.7.3.1 Median changes from baseline for short term placebo controlled Phase II/III trials (from sponsor's electronic submission)

	Ziprasidone			Haloperidol			Placebo		
	N	Median Baseline	Median Change From Baseline To Last Obs	N	Median Baseline	Median Change From Baseline To Last Obs	N	Median Baseline	Median Change From Baseline To Last Obs
Standing									
Systolic BP (mmHg)	674	114.5	0.0	83	120.0	1.0	260	118.0	0.0
Diastolic BP (mmHg)	674	78.0	0.0	83	80.0	0.0	260	80.0	0.0
Heart Rate (bpm)	669	88.0	0.0	83	86.0	0.0	256	88.0	0.0
Sitting									
Systolic BP (mmHg)	690	118.0	0.0	84	120.0	2.0	265	118.0	0.0
Diastolic BP (mmHg)	690	76.0	0.0	84	78.0	0.0	265	76.0	0.0
Heart Rate (bpm)	690	80.0	0.0	84	80.0	1.5	265	80.0	0.0
Supine									
Systolic BP (mmHg)	1	120.0	-8.0						
Diastolic BP (mmHg)	1	78.0	-10.0						
Heart Rate (bpm)	1	70.0	2.0						
Temperature (C)	243	36.6	0.0				99	36.6	0.1
Weight (kg)*	622	75.0	0.5	74	79.4	0.0	227	75.8	0.0

N is the total number of subjects with a baseline observation and at least one observation while on study treatment or within six days after the last day of study treatment for the given vital sign parameter.
* Kruskal-Wallis test yielded a significant association at the .05 level of alpha by using the RANK and ANOVA procedures.
Protocols: 104,106,114,115

Appendix 8.1.7.3.2 Incidence of Clinically Significant Changes in Vital Signs in Short-term Placebo Controlled Studies:

	Ziprasidone			Haloperidol			Placebo		
	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed
Standing Systolic BP (mmHg)									
Increase (BP>180, CHG>=20)	674	1	0.1	83	0	0.0	260	1	0.4
Decrease (BP<90, CHG<=-20)	674	22	3.3	83	3	3.6	260	9	3.5
Standing Diastolic BP (mmHg)									
Increase (BP>105, CHG>=15)	674	14	2.1	83	1	1.2	260	4	1.5
Decrease (BP<50, CHG<=-15)	674	3	0.4	83	3	3.6	260	3	1.2
Standing Heart Rate (bpm)									
Increase (BP>120, CHG>=15)	669	21	3.1	83	2	2.4	256	9	3.5
Decrease (BP<50, CHG<=-15)	669	3	0.4	83	1	1.2	256	0	0.0
Sitting Systolic BP (mmHg)									
Increase (BP>180, CHG>=20)	690	1	0.1	84	0	0.0	265	1	0.4
Decrease (BP<90, CHG<=-20)	690	11	1.6	84	3	3.6	265	6	2.3
Sitting Diastolic BP (mmHg)									
Increase (BP>105, CHG>=15)	690	12	1.7	84	1	1.2	265	7	2.6
Decrease (BP<50, CHG<=-15)	690	5	0.7	84	0	0.0	265	2	0.8
Sitting Heart Rate (bpm)									
Increase (BP>120, CHG>=15)	690	1	0.1	84	0	0.0	265	2	0.8
Decrease (BP<50, CHG<=-15)	690	2	0.3	84	3	3.6	265	2	0.8
Supine Systolic BP (mmHg)									
Increase (BP>180, CHG>=20)	1	0	0.0	0	0		0	0	
Decrease (BP<90, CHG<=-20)	1	0	0.0	0	0		0	0	
Supine Diastolic BP (mmHg)									
Increase (BP>105, CHG>=15)	1	0	0.0	0	0		0	0	
Decrease (BP<50, CHG<=-15)	1	0	0.0	0	0		0	0	
Supine Heart Rate (bpm)									
Increase (BP>120, CHG>=15)	1	0	0.0	0	0		0	0	
Decrease (BP<50, CHG<=-15)	1	0	0.0	0	0		0	0	
Weight (kg)									
Increase (CHG>=7%)*	622	61	9.8	74	4	5.4	227	9	4.0
Decrease (CHG<=-7%)	622	16	2.6	74	1	1.4	227	7	3.1

N is the total number of subjects with a baseline observation and at least one observation while on study treatment or within six days after the last day of study treatment for the given vital sign parameter.
To be a clinically significant change, a value has to both meet the criterion value and represent a change from baseline of at least the magnitude noted at any time during the study treatment or within the six days after the study treatment.
* Fisher exact two-tailed test yielded a significant association at the .05 level of alpha.
Protocols: 104,106,114,115

Appendix 8.1.8.3.1 Mean and Mean Change values of electrocardiogram variables comparing baseline and end of treatment with ziprasidone and placebo in short term placebo controlled Phase II/III trials (from sponsor's submission dated 11/13/97).

Table N.5.23.1 (Short Term) - Centrally Read 104,106,114, & 115 — Page 1 of 2
Change from Baseline to Maximum Reading Value in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies
By BID Dose - Centrally Read Date

	Placebo			40mg BID			40mg BID			60mg BID			80mg BID		
	N	Base Mean	Max Mean**	N	Base Mean	Max Mean**	N	Base Mean	Max Mean**	N	Base Mean	Max Mean**	N	Base Mean	Max Mean**
*QTc int	250	399.0	4.3	230	396.9	8.6	138	397.6	12.6	111	398.0	15.2	100	394.6	19.8
QT int	250	348.6	7.6	230	354.6	5.0	138	351.2	7.5	111	352.6	15.1	100	352.4	14.4
Heart Rate	250	80.4	4.5	230	76.6	7.8	138	78.6	6.6	111	78.5	5.4	100	76.7	6.7
PR int	250	149.2	3.4	230	148.8	4.3	138	148.4	1.9	111	149.2	2.6	100	150.0	2.5
QRS int	250	86.1	1.6	230	86.6	1.5	138	86.3	1.3	111	86.8	1.2	100	85.5	1.8

(CONTINUED)
Protocols: 104,106,114,115
*QTc int = QT int/SQRT(60/(Heart Rate))
** Maximum change from baseline for each subject where baseline is the last ECG taken before the first day of study treatment.
Total Changed = number of subjects with both a baseline ECG value and post-baseline value within six days after the last day of study treatment.
Date of table generation: 12NOV97.

Table N.5.23.1 (Short Term) - Centrally Read 104,106,114, & 115 — Page 2 of 2
Change from Baseline to Maximum Reading Value in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies
By BID Dose - Centrally Read Date

	>=100mg BID			Haloperidol		
	N	Base Mean	Max Mean**	N	Base Mean	Max Mean**
*QTc int	77	402.7	15.0	76	400.2	4.1
QT int	77	354.9	17.1	76	357.3	7.1
Heart Rate	77	78.8	4.5	76	76.8	4.4
PR int	77	148.3	1.6	76	150.9	3.1
QRS int	77	87.3	1.2	76	87.1	0.9

Protocols: 104,106,114,115
*QTc int = QT int/SQRT(60/(Heart Rate))
** Maximum change from baseline for each subject where baseline is the last ECG taken before the first day of study treatment.
Total Changed = number of subjects with both a baseline ECG value and post-baseline value within six days after the last day of study treatment.
Date of table generation: 12NOV97.

Appendix 8.1.8.3.2 ECG: percent of subjects who met sponsors criteria for clinically significant changes in short term placebo controlled studies. (from sponsor's submission dated 11/13/97)

Table N.5.22 [Short Term] - Centrally Read 104.106.114. & 115 — Page 1 of 2
Incidence of Clinically Significant Changes in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies
By BID Dose - Central Reader Data

		Placebo			<40mg BID			40mg BID			60mg BID			80mg BID		
		N	Total Changed	%	N	Total Changed	%	N	Total Changed	%	N	Total Changed	%	N	Total Changed	%
*QTc int	>=480 msec	251	0	0	233	0	0	130	0	0	112	1	0.9	100	0	0
	>=500 msec	251	0	0	233	0	0	130	0	0	112	0	0	100	0	0
	>=75 msec increase **	250	0	0	230	0	0	130	0	0	111	0	0	100	0	0
	>=10% increase **	250	11	4.4	230	12	5.2	130	11	8.0	111	12	10.8	100	16	16.0
	>=15% increase **	250	2	0.8	230	1	0.4	130	1	0.7	111	1	0.9	100	3	3.0
	>=20% increase **	250	0	0	230	0	0	130	0	0	111	0	0	100	0	0

(CONTINUED)
Protocols: 104.106.114.115
*QTc int = QT int/SQRT(60/(Heart Rate))
** From baseline where baseline is the last ECG taken before the first day of study treatment.
Total Changed = number of subjects with an ECG reading meeting criteria while on study treatment or within six days after the last day of study treatment.
Date of table generation: 21OCT97.

Table N.5.22 [Short Term] - Centrally Read 104.106.114. & 115 — Page 2 of 2
Incidence of Clinically Significant Changes in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies
By BID Dose - Central Reader Data

		>=100mg BID			Haloperidol		
		N	Total Changed	%	N	Total Changed	%
*QTc int	>=480 msec	77	0	0	76	0	0
	>=500 msec	77	0	0	76	0	0
	>=75 msec increase **	77	0	0	76	0	0
	>=10% increase **	77	11	14.3	76	4	5.3
	>=15% increase **	77	1	1.3	76	0	0
	>=20% increase **	77	0	0	76	0	0

Protocols: 104.106.114.115
*QTc int = QT int/SQRT(60/(Heart Rate))
** From baseline where baseline is the last ECG taken before the first day of study treatment.
Total Changed = number of subjects with an ECG reading meeting criteria while on study treatment or within six days after the last day of study treatment.
Date of table generation: 21OCT97.

...idix 8.1.9.2a Extrapyramidal Symptoms Assessment for Studies 114 an... .15 using the Simpson-Angus Rating Score (adapted from sponsor's submission)

Simpson-Angus Rating Scale Score** - Percent of Subjects with a Postbaseline Change by Visit - All Subjects Not Taking Benztropine, Observed Cases
Ziprasidone Protocol 114

		Day 7*	Day 21	Day 42	Last
Ziprasidone, 40 mg BID	Increase	19.8	30	16.3	15.7
	Decrease	34.6	36.7	48.8	42.2
	No Change	45.7	33.3	34.9	42.2
	N	81	60	43	83
Ziprasidone, 80 mg BID	Increase	19.7	27.9	39.1	32.5
	Decrease	18.4	20.6	23.9	23.4
	No Change	61.8	51.5	37	44.2
	N	76	68	46	77
Placebo	Increase	21.1	16.4	16.7	21.5
	Decrease	23.7	24.6	40.5	25.3
	No Change	55.3	59	42.9	53.2
	N	76	61	42	79

**Simpson-Angus Rating Scale Score equals the sum of SARS items 1 through 10.
*Day 7 = visit 7; Day 21 = visit 21; Day 42 = visit 42; Last = last visit, planned or unplanned.

Simpson-Angus Rating Scale Score** - Percent of Subjects with a Postbaseline Change by Visit - All Subjects Not Taking Benztropine, Observed Cases
Ziprasidone Protocol 115

		Day 7*	Day 21	Day 42	Last
Ziprasidone, 20 mg BID	Increase	23.3	20.9	30.3	27
	Decrease	26.7	23.3	30.3	28.6
	No Change	50	55.8	39.4	44.4
	N	60	43	33	63
Ziprasidone, 60 mg BID	Increase	15.3	16.3	12.5	20
	Decrease	28.8	40.8	37.5	33.3
	No Change	55.9	42.9	50	46.7
	N	59	49	32	60
Ziprasidone, 100 mg BID	Increase	17	20.5	20	21.3
	Decrease	25.5	41	36.7	38.3
	No Change	57.4	38.5	43.3	40.4
	N	47	39	30	47
Haloperidol	Increase	27.8	33.3	35	45
	Decrease	8.3	10	15	15
	No Change	63.9	56.7	50	40
	N	36	30	20	40
Placebo	Increase	15.4	20	4.8	13
	Decrease	21.2	22.9	23.8	25.9
	No Change	63.5	57.1	71.4	61.1
	N	52	35	21	54

**Simpson-Angus Rating Scale Score equals the sum of SARS items 1 through 10.
*Day 7 = visit 7; Day 21 = visit 21; Day 42 = visit 42; Last = last visit, planned or unplanned.

Appendix 8.1.9.2b Akathisia Assessment for Studies 114 and 115 using the Barnes Akathisia Scale (adapted from sponsor's submission)

rnes Akathisia Scale Global Score - Percent of Subjects with a Postbaseline Change by Visit -
l Subjects Not Taking Beta-Blockers, Observed Cases
prasidone Protocol 114

		Day 7*	Day 21	Day 42	Last
iprasidone, 0 mg BID	Increase	20.6	12.5	15.7	16.3
	Decrease	12.4	16.7	17.6	18.4
	No Change	67	70.8	66.7	65.3
	N	97	72	51	98
iprasidone, 0 mg BID	Increase	13	19.5	13.8	12.9
	Decrease	18.5	17.1	22.4	18.3
	No Change	68.5	63.4	63.8	68.8
	N	92	82	58	93
lacebo	Increase	11.1	12.7	9.3	8.2
	Decrease	23.5	27	25.6	27.1
	No Change	65.4	60.3	65.1	64.7
	N	81	63	43	85

y 7 = visit 7; Day 21 = visit 21; Day 42 = visit 42; Last = last visit, planned or unplanned.

Barnes Akathisia Scale Global Score - Percent of Subjects with a Postbaseline Change by Visit -
All Subjects Not Taking Beta-Blockers, Observed Cases
Ziprasidone Protocol 115

		Day 7*	Day 21	Day 42	Last
Ziprasidone, 20 mg BID	Increase	17.9	10.5	11.1	13.8
	Decrease	14.1	21.1	20	21.3
	No Change	67.9	68.4	68.9	65
	N	78	57	45	80
Ziprasidone, 60 mg BID	Increase	14.7	16.4	8.3	14.5
	Decrease	14.7	10.9	13.9	10.1
	No Change	70.6	72.7	77.8	75.4
	N	68	55	36	69
Ziprasidone, 100 mg BID	Increase	18.4	9.5	9.3	14.5
	Decrease	6.6	17.5	18.6	14.5
	No Change	75	73	72.1	71.1
	N	76	63	43	76
Haloperidol	Increase	29	29.1	23.1	29.9
	Decrease	12.9	21.8	20.5	19.4
	No Change	58.1	49.1	56.4	50.7
	N	62	55	39	67
Placebo	Increase	14.3	18.6	8.3	16.4
	Decrease	21.4	20.9	29.2	27.4
	No Change	64.3	60.5	62.5	56.2
	N	70	43	24	73

*Day 7 = visit 7; Day 21 = visit 21; Day 42 = visit 42; Last = last visit, planned or unplanned

FEB 3 1998

Review of Clinical Data

Review of Data Quality, Coding, All Cause Mortality and Sudden Deaths

NDA:	**NDA 20-825**
Sponsor:	**Pfizer**
Drug:	**Ziprasidone**
Route of Administration:	**Oral**
Reviewers:	**Gerard Boehm, M.D., M.P.H.** **James F. Knudsen, M.D., Ph.D.**
Author:	**Gerard Boehm, M.D., M.P.H.**
Review Completion Date:	**2/3/98**

The objectives of this review are to evaluate the methods of coding and overall quality of the data and to review all cause and cause specific mortality with emphasis on sudden deaths in ziprasidone trials. This review covers information presented in the NDA and the 4 month safety update. I used the results from Dr. Knudsen's evaluation of the data quality and coding for this report.

Methods

Accuracy of the database
To verify accuracy of the data submitted with the NDA, we cross checked the data for deaths and cardiac adverse events presented in line listings/tabulations, narrative summaries, and CRF's. Specifically, the sources were examined for inconsistencies and omissions.

To evaluate the coding process, subsumed investigator verbatim terms for adverse events were compared with the preferred terms included in appendix VI. In addition, the events that were coded with selected preferred terms were reviewed in more detail. Using narrative summaries and CRF's, the adverse events coded with the preferred terms arrhythmia, tachycardia, bradycardia, syncope, hypotension, postural hypotension, heart arrest and circulation failure were compared across sources to determine if the coding process resulted in appropriate groupings.

Deaths
The overall mortality rates were compared between ziprasidone group and the comparator groups using the number of deaths that occurred within 30 days of the last

exposure to drug for deaths presented in the NDA and safety update. The ziprasidone mortality rate was also compared to the mortality rates of other recently approved antipsychotic medications.

I reviewed and summarized the narrative summaries and the CRF data for ziprasidone patient deaths. I then classified the deaths into 4 categories. Those deaths for which there was a definite external cause (ex. suicide jumped in front of a train) were placed in the first category. Those deaths with a probable external cause, but where there remains some question about the possibility of a sudden death (ex. a car accident where the driver could have experienced sudden death) were placed in the second category. The third category contains deaths that appear to be related to an underlying process (ex. cancer or pneumonia). The last category contains the deaths that occurred suddenly, noting which deaths were explained by an underlying process (example sudden death with ruptured aneurysm discovered on autopsy). Using this scheme, I calculated an external cause (definite + probable) and sudden death rate for the NDA data alone, and for the combined NDA and safety update information. The calculated sudden death rate for ziprasidone was compared to the sudden death rate for recently approved antipsychotic medications.

Results

Approach to Safety, Data Accuracy and Specificity of the AE Coding

The sponsor defined treatment emergent adverse events as 1) events not present at baseline or during the baseline period and that occurred after treatment began 2) events that were present at baseline but increased in severity after beginning treatment. AE surveillance occurred at each study visit. Investigators recorded observed or volunteered AE's that occurred during the treatment period or within 6 days after the last day of treatment. The sponsor translated investigator verbatim terms to preferred terms using the COSTART dictionary. The AE's were presented in tabular form with information about treatment emergence, body system classification, investigator assessment of severity (mild, moderate or severe) and causality. When an event for a patient was reported with more than one severity, the summary tables reported the greatest severity recorded by the investigator. Events without investigator assessments of severity were classified as severe.

The investigator verbatim terms listed in the CRF's of the patients who died, had serious cardiovascular adverse events, or dropped out due to cardiac related events, were congruent with those listed in the tabulations/data listings and included in the narrative summaries. The narrative summaries often provided more clinical detail, particularly about past medical history. Additionally, the narrative summaries often cited autopsy data that were not included in the CRF. The CRF's were limited for clinical information with the exception that they contained vital sign, ECG, and laboratory data which was less complete in the narrative summaries.

In general, the COSTART coding of the investigator verbatim terms was appropriate. The sponsor provided a comprehensive line listing of adverse events aggregated across all Phase II/III studies which included the investigator verbatim and coded preferred term for each report. With few exceptions, the sponsor's coding practices were neither excessively narrow nor broad. The sponsor may have been too overly inclusive in deciding what to subsume under the preferred term postural hypotension. The verbatim terms orthostatic hypotension, dizziness on standing, and lightheadedness with standing were subsumed under the preferred term postural hypotension. This approach increases the sensitivity of the coding for detecting patients with orthostatic changes in blood pressure but probably lessens the specificity.

Orthostatic change in pulse, irregular pulse, and arrhythmia were subsumed under the preferred term arrhythmia, whereas orthostatic tachycardia and elevated pulse were subsumed under the preferred term tachycardia. This grouping probably decreased the ability to detect orthostatic changes by report of change in pulse. Since there are other parameters for detecting orthostatic changes (blood pressure change, symptoms) these coding practices probably had minimal impact on the ability to identify this event. Loss of consciousness and fainting were appropriately subsumed under the preferred term syncope and not under hypotension.

The data quality for death and cardiovascular adverse events was adequate. With few exceptions, the sponsor's coded terms accurately reflected the investigator verbatim terms. These data allow an accurate assessment of the events occurring during the ziprasidone development program.

Deaths

There were 32 deaths reported with the NDA and safety update. Eighteen deaths occurred within 30 days of the last exposure to ziprasidone. One of these deaths (suicide from the safety update) was from the Japanese database which was maintained separately and did not contribute to the person time used to calculate rates (p.5 Safety Update). That death is not included in the following discussions or the mortality rate calculations.

In the original NDA submission, there were 14 deaths that occurred within 30 days of the discontinuation of ziprasidone. The all cause mortality rate for this population was 2.2/100PY (14/626PY). The safety update included 3 additional deaths within 30 days of last exposure and almost 150 additional patient years of exposure. The all cause mortality rate including the safety update data was 2.2/100PY (17/772PY). This mortality rate is higher than the rates observed for other recently reviewed antipsychotic medications.

The sponsor also provides a calculation of crude mortality for the comparator groups through the safety update. The cumulative crude mortality rate for the placebo exposed group is 9.6/100 patient years exposure (5 deaths in 52 patient years). The crude mortality rate observed in patients exposed to haloperidol was 2.3 per 100 patient years (3 deaths in

131 patient years) and for risperidone 0.95 per 100 patient years (1 death in 105 patient years).

Cause Specific Mortality

Cardiovascular related deaths were more commonly observed in ziprasidone treated individuals compared to patients receiving placebo or active comparator medications. Ten of the 17 deaths that occurred within 30 days of the last dose of ziprasidone (including the safety update) are possibly cardiovascular related. These deaths included diagnoses such as cardiac arrest, ruptured abdominal aortic aneurysm and several unwitnessed, and sudden deaths without clear diagnoses that are suspicious for cardiovascular events. The other causes of death reported in ziprasidone trials were suicide (3), drowning (2), aspiration (1), and accident(1). The deaths in the placebo patients were from pneumonia (3), extradural hematoma, and suicide. In the haloperidol group there were 2 suicides and a post operative MI leading to death. The death in the risperidone group was due to aspiration of food.

Ziprasidone and Sudden Deaths

In the sponsor's review, a death was "sudden" if it occurred within 24 hours of the onset of symptoms directly associated with the death. Including safety update data, the sponsor classified 7 deaths as sudden, giving a sudden death rate of 0.9 per 100 PY exposure (7 sudden deaths in 772 patient years exposure). In my opinion, 6 deaths (35%) had an external cause (definite + probable) and 11 deaths (65%) were sudden. One of the sudden deaths included with the safety update was explained at autopsy (ruptured abdominal aortic aneurysm).

Considering only the NDA death information (not including the safety update), I felt that 6 deaths (43%) had an external cause (definite + probable), and 8 deaths (57%) were sudden (see appendix). The death rate due to external cause was 0.9 per 100PY (6/626) and the sudden death rate was 1.3/100PY (8/626).

A combined sudden death rate was calculated from the NDA data for several recently approved antipsychotic medications. For these 3 drugs, there were 6 sudden deaths in 2496 patient years exposure giving a sudden death rate of 2 per 1000PY. The population in the phase II/III ziprasidone trials was similar to the populations studied in other recently reviewed antipsychotic medications with respect to mean age (39.6), age range (7-82), percent males (72%) and percent caucasians (76%).

Discussion

Because the placebo and active comparator experience within the NDA was limited, the death rate information for ziprasidone was compared with the rates observed for other recently reviewed antipsychotic medications. The all cause mortality rate for ziprasidone was higher than the rate observed with the other medications. After applying the

classification scheme described above, the causes of death appeared to differ from the causes observed with the other medications. Sudden deaths were 6 times more common for the ziprasidone group compared to the rates for the other medications. The rate of deaths with external, explained causes in the ziprasidone development program was similar to the rates estimated for other recently reviewed drugs.

The classification of sudden deaths in these analyses is a function of the quality of available data and reviewer opinion. The quality of information is dependent, in large part, on the data collection methods employed by the sponsor and the investigators. One must consider that variability in the quality of data across NDA's could lead to a classification bias resulting in the observed differences in mortality rates.

Development programs are usually separated by place and time and differ with respect to populations studied, inclusion/exclusion criteria, and concomitant medications allowed. Any or all of these factors could have an influence on the observed sudden death rate. Therefore, comparisons across NDA's should be interpreted cautiously and in the context of all available safety data.

Conclusions

1. The data quality and approach to coding were adequate for the purpose of this review.
2. The all cause mortality rate was higher for ziprasidone compared to rates for other recently reviewed antipsychotic medications.
3. The sudden death rate for ziprasidone is 6 times higher than that for combined data from recently reviewed NDA's.

Because of potential differences in available data and in the drug development programs, these mortality rate comparisons are not conclusive evidence for determining if there is increased risk associated with exposure to ziprasidone. The signal of increased sudden deaths may become an important complementary piece of evidence in the presence of other safety data. One concern that has potential relevance to this finding is an apparent dose dependent QTc prolonging effect associated with ziprasidone in the STFDPC study population.

Gerard Boehm M.D., M.P.H.

2-3-98
Agree
/S/

cc:HFD-120\Boehm\Burkhart\Laughren\Leber \Glass

Appendix
Summaries for the 17 deaths that occurred within 30 days of last exposure to drug from the ziprasidone NDA and the safety update.

Category 1 (Definite external cause)
128-302E-159-0029 Suicide, falling under a train.
128-116B- 694-0004 Suicide, hanging.
128-108-609-0381 Suicide, gunshot.

Category 2 (Probable external cause)
128-117-706-0529 This 40 YO male with a past medical history significant for bronchitis, took ziprasidone for 54 days and the last recorded dose was 160mg per day. Four days after self-discontinuing ziprasidone, he underwent a sleep deprived EEG to evaluate complaints of amnesia that began following an assault. He left the testing site after 30 hours of sleep deprivation and drove himself home. Two hours after leaving the site, he drove his car off a cliff and died. The autopsy listed asphyxiation due to salt water drowning as the cause of death. Concomitant medications at the time of death included propranolol, antacids, and clonazepam. The investigator felt that this was an accidental death caused by sleep deprivation. There sponsor noted that the patient had plans for the future and there was no suicide note.

128-117-687-0317 This 51 YO male took ziprasidone for 205 days at a dose of 120mg daily. He died from injuries sustained from a fall from his 10th floor balcony. The patient was taking no other medications at the time of death. His last study visit was 9 days prior to his death and he appeared to be doing well and had plans for the future. The sponsor notes that on the day of his death he went to a church crisis center and appeared intense. The sponsor states that the coroner initially felt this was a suicide but was reconsidering that initial conclusion. The investigator felt that this was an accident.

128-303-260-0156 This 46 YO male took ziprasidone for 7 days and the last recorded dose was 120mg daily. His body was found in a river 5 days after leaving a hospital where he was an inpatient. He was taking no other medications at the time of his death. The autopsy listed drowning as the cause of death. He had no prior history of suicidal ideation or suicide attempts. The investigator felt that this was possibly a suicide.

Category 3 (Underlying disease)

Category 4 (Sudden deaths)

128-308-035-0003 *This 63 YO male was treated with ziprasidone for 75 days and the last recorded dose was 80mg daily. While at a lunch club, he collapsed and died suddenly. He was taking no other medications at the time of his death. The coroners report listed ruptured abdominal aortic aneurysm as the cause of death.

128-115-694-0394 This 43 YO male took ziprasidone for 16 days and the last recorded dose was 40mg daily. He withdrew consent and left the study. Subsequently, he had 2 psychiatric hospitalizations for severe generalized anxiety and tardive dyskinesia. He also had been seen in an ER for breathing difficulties and was discharged without prescribed treatment. Thirty days after stopping ziprasidone, he awoke with difficulty breathing and while getting ready to go to the hospital, he vomited. He was found unconscious by his sister, and did not respond to resuscitative measures. The coroner listed asphyxia due to aspiration of vomit as the cause of death. He was taking risperidone, lorazepam, and clonazepam at the time of death.

128-116B-659-0001 This 44 YO female took ziprasidone for 40 days and the last recorded dose was 80mg daily. The study drug was discontinued due to lack of efficacy. While still taking drug, she experienced chest pain. Cardiac work-up (including stress echo) was normal. A GI work-up revealed mildly elevated LFT's and non specific gastritis. Thirteen days after stopping ziprasidone she was admitted to a hospital for hematemesis and endoscopy revealed gastritis with H. pylori. She was treated with clarithromycin, omeprazole, and cisapride. Five days later she was treated in an ER for panic attack. Three days after the ER visit (24 days after stopping ziprasidone) she was found dead in bed. Medications at the time of death included buspirone, sucralfate, acetaminophen, lorazepam, omeprazole, clarithromycin, and cisapride. An autopsy report was not available, but the subject's attending physician learned of a possible atrial myxoma from the ME's office.

128-304E-0193-0379 This 52 YO male took ziprasidone for 221 days and the last recorded dose was 80mg daily. The patient was found dead in bed. At the time of death, the patient was taking acetaminophen as needed for headaches. The physician who attempted resuscitation felt that death was due to cardiac arrest with possible myocardial infarction. Multiple ECG's recorded for the study did not show ischemic changes. The patient had 3 cardiovascular disease risk factors (male, tobacco use and sedentary lifestyle). There was no autopsy.

128-301-311-0977 This 28 YO female received ziprasidone for 62 days and the last recorded dose was 120mg daily. The drug was stopped for insufficient response. On the day that ziprasidone was stopped, the patient had an end study ECG suggesting subendocardial ischemia. Because of this finding, she was transferred to an internal medicine service in another hospital. She complained of a substernal pinching sensation. The physician did not think this symptom was due to a cardiac disorder. The admitting diagnoses were schizophrenic psychosis, somatic asthenia, chronic disturbance of food intake, and arrhythmia without clear cause. The patient was started on thioridazine, nitrazepam, and a liquid diet supplement. The next day she was noted to have orthostatic symptoms and an ECG reportedly showed sinus arrhythmia at a rate of 58 beats per minute. She died the next day (2 days after stopping ziprasidone). Concomitant medications were biperiden, temazepam, thioridazine, fresubin liquide, nitrazepam, duovit, and vitamin B complex. At the time of death, she was described as cachetic and malnourished (height 5'6" and weight 42kg). An autopsy revealed atrophic and

dystrophic heart muscle fibers which could be associated with toxins, infection, or metabolic abnormalities. A consultant pathologist was unable to determine the cause of death and did not find any changes in the myocardium suggesting a specific disease or drug reaction. A consultant cardiologist reviewed the ECG tracings and felt the bradycardia and T-wave abnormalities were consistent with abnormalities seen with malnutrition.

128-108-607-0305 This 46 YO male took ziprasidone for 61 days at a dose of 80mg daily. He had a past medical history significant for asthma, COPD, PUD, gastroenteritis, microhematuria, and gallstones. During the study, he had a hospitalization for pneumonia and gastroenteritis. Approximately 1 month later, he was found dead in a chair on his front porch presumably after mowing his lawn on a hot day. Concomitant medications at the time of death were beclamethasone, metaproterenol, and Maalox. Autopsy revealed acute and chronic asthmatic bronchitis and granulomatous myocarditis. The liver and brain each had a granulomma-like lesion. The conclusion of the autopsy was that the patient died from asthmatic bronchitis possibly exacerbated by lawn mowing. An independent pathology consultant interpreted the histologic slides as focal myocarditis of unknown etiology. The sponsor admitted that the exact cause of death in this case was uncertain and offered several possible explanations(asthmatic bronchitis, possible heat related illness, myocardial inflammation).

128-116B-508-0001 This 54 YO male took ziprasidone for 72 days, and his last recorded dose was 120mg daily. His past medical history was significant for hypertension, COPD, GERD, constipation, and peripheral vascular disease. He was found dead in his hospital bed. Concomitant medication at the time of death included Procardia XL, ipratropium, triamcinolone, albuterol, docusate lorazepam, aspirin, disulfiram, propranolol, and ranitidine. The sponsor noted that the patient had an episode of chest pain approximately 1 month prior to death. ECG done at that time was reportedly normal. An autopsy revealed severe generalized atherosclerosis, cerebral artery disease, visceral congestion, COPD, cardiac hypertrophy, and vocal cord congestion. The investigator felt that the death was due to atherosclerosis.

128-108-592-0750 *This 39 YO female received ziprasidone for a total of 7 days and the last recorded dose of the drug was 120mg daily. She had a past medical history significant for diabetes mellitus type II, tobacco abuse and alcohol abuse. She was found dead in her apartment. The diagnosis, according to the ME, was chronic alcoholism with hepatic steatosis, supported by a clinical history of alcohol abuse. The sponsor noted that decomposition of the body made a final post-mortem diagnosis difficult. The investigator attributed the death to alcohol abuse and DKA (no supporting blood glucose or pH data provided).

128-302E-319-0375* This 48 YO male took ziprasidone for 162 days and the last recorded dose was 120mg. He had a past medical history significant for hypertension. The investigator discontinued ziprasidone because of increasing psychopathology and started the patient on haloperidol. The following day he was found dead in his apartment.

He had a prior history of water intoxication and associated hyponatremia. The sponsor stated that the autopsy report was not available. A preliminary opinion from the ME attributed the death to cardiac arrest secondary to sodium depletion associated with water intoxication. Supporting data (serum sodium concentration) was not provided.

128-303-197-0299 This 79 YO female took ziprasidone for 30 days and the last recorded dose was 80mg daily. She had a past medical history significant for ischemic heart disease and atrial fibrillation. Thirty days after discontinuing ziprasidone, she experienced a presumed cardiac arrest. An autopsy was not performed.

128-105-534-0021 This 70 YO female took ziprasidone for 5 days and the last recorded dose was 2mg daily. She was treated with ziprasidone for behavioral disturbances associated with dementia. She had a past medical history significant for COPD, right bundle branch block, tobacco abuse, hypothyroidism, and hip fracture. On the 5th day of treatment, she developed shallow respirations and diaphoresis. She was taken to the hospital, arrested and died. The death certificate listed acute cardiopulmonary arrest due to arteriosclerotic cardiovascular disease as the cause of death. Concomitant medications at the time of death included atenolol, ranitidine, levothyroxine, potassium chloride, theophylline, heparin, albuterol, ipratropium bromide, diltiazem, furosemide, docusate, mycolog, and glypizide.

*Indicates death was identified in the safety update.

APPEARS THIS WAY
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(7661)

JAN 11 2000

Review of Clinical Data

Preliminary Review of Study 054

IND: [ ]

Sponsor: **Pfizer**

Drug: **Ziprasidone**

Route of Administration: **PO**

Reviewer: **Greg Burkhart, M.D., M.S.**

Review Completion Date: **January 11, 2000**

S 1-11-00

Study 054 was an open-label study comparing QT interval duration between patients randomly assigned to ziprasidone, risperidone, quetiapine, olanzapine, thioridazine, or haloperidol. Pfizer initiated the study to address concerns raised in the June 17, 1998 not-approvable letter about ziprasidone's capacity to increase cardiac repolarization.

We received a summary of the findings from study 054 on December 6, 1999 and the full study report on January 3, 2000. My review is preliminary because the study report was incomplete. It relied upon the square root method of correcting the QT interval for heart rate. Dr. Laughren, prior to completion of study 054, had informed Pfizer that the square method causes a bias particularly for drugs that increase the heart rate. This bias was discovered after study 054 was in progress but is a significant concern since many antipsychotics increase the heart rate. While Pfizer provided summary data for analyses that used other more appropriate methods of correcting the QT in a separate submission, they will not provide a full presentation and discussion of these findings until they submit their response to the not-approvable letter.

Study 054 began with a 7-day out-patient period during which pre-existing antipsychotic medication was tapered. Patients then entered the treatment facility for a 7-day washout/ baseline period. Following baseline data collection, patients were titrated to the maximum marketed dose for their assigned drug (80 mg BID for ziprasidone) and observed at steady state. (Drop-outs were replaced.) Because of different kinetic properties, the duration of the dose escalation period varied by drug group with ziprasidone and thioridazine having the shortest (10 days) and risperidone having the longest (18 days). Once patients had achieved steady state and ECGs were collected, a protocol-specified metabolic inhibitor was added to each drug group and observation continued. After ECGs were collected in the presence of the metabolic inhibitor, treatment was tapered and terminated for all patients.

cc: IND [ ]
NDA 20-825
HFD-120 Burkhart, Katz, Laughren, Glass, Abrahamson

Daily ECGs were taken for the last 3 days of baseline. A single ECG was taken at day 2 of the dose escalation period and daily ECGs were taken for 3 days at steady state. Pfizer timed the 4 ECGs taken during exposure to the estimated c max for each drug. Daily ECGs were also collected for 3 days in the presence of the metabolic inhibitor. A blinded reviewer read all ECGs to manually measure the QT interval. The analysis focused on the change from baseline that occurred at steady state and any change occurring in the presence of the metabolic inhibitor.

I have attached some of the tables and figures from the study report and those provided in a separate fax. Figure 2.1 shows that at steady state (period 3) all drugs but haloperidol caused an increase in the heart rate. This certainly raises the possibility that the square root correction method would not standardize the QT, and could more importantly, cause a biased comparison with haloperidol. (I am showing the data for completers, but the findings are the same when using all randomized patients.)

As a reminder, the haloperidol group was added to the study at the insistence of the FDA because we were aware of a large amount of data across several NDAs showing that oral haloperidol had no effect on the QT when compared to placebo. (One study was a 7-arm study that evaluated three doses of haloperidol.) Thus, it was our view at the start of study 54 that haloperidol would serve as the control arm providing a formal basis for comparison. We also recommended that thioridazine be added as a treatment group since there was some data suggesting that it prolonged the QT and there were also cases of TDP reported in the post-marketing literature.

Figure 3.1 shows the change from baseline in the uncorrected QT. For drugs that cause an increase in heart rate, one would expect the QT to decrease, as occurred with risperidone, olanzapine, and quetiapine. However, for thioridazine and ziprasidone, both of which caused an increase in heart rate, the QT increased. (Haloperidol also had an increase in QT, but the heart rate decreased from baseline in this group so that the increase in QT would be expected.)

Figure 1.1.1 shows the square root corrected QTCs by treatment group whereas tables 6b and 6c show QTCs using other methods of correction that do a better job of standardizing the QT for heart rate. Focusing on tables 6b and 6c, it seems fairly clear that there are only two between group differences in study 054 when using haloperidol as the basis for comparison. Both ziprasidone and thioridazine clearly caused a prolongation in the QT with the size of the effect much more impressive for thioridazine. The effect for ziprasidone appears to be about 10 msec, which was similar to that observed in the NDA. (Pfizer did not provide any statistical testing of these findings, but by examining the 95% CIs, one can reasonably conclude that there is significant statistical evidence of a difference when comparing either ziprasidone or thioridazine with haloperidol; the evidence for thioridazine being much stronger since there is no overlap in CIs.)

After seeing the findings from study 054, I believe there are three significant conclusions. First, ziprasidone affects cardiac repolarization within its proposed dose range whereas

risperidone, quetiapine, and olanzapine do not have such an effect, at least within their marketed dose range. Second, the size the effect attributable to ziprasidone is about 10 msec, which is similar to that observed in the ziprasidone NDA. Finally, thioridazine clearly has a large effect upon cardiac repolarization that is almost certainly clinically significant and life threatening. Several cases of TDP have been documented with thioridazine use in the literature and significantly lower doses of thioridazine than that studied in 054 have also been shown to prolong the QT.

I should also point out that patients in all dose groups seemed to tolerate the study fairly well. There were no deaths or serious events on drug, and no reported cases of TDP or syncope. One patient on thioridazine had an adverse event reported as "QT prolonged". The groups were also fairly comparable in the rate of discontinuation. For ziprasidone, 35 patients were randomized with 31 completing the study.

Pfizer appears to have concluded that study 054 shows that all drugs in the study prolonged the QTC. This conclusion is apparently based upon the fact that there was a positive change from baseline in QTC observed in each drug group. However, in my view, the empirical evidence does not support this conclusion. An additional control group such as placebo or even a lower dose of haloperidol that experienced significantly less change in QTC during study would be necessary to justify such a conclusion.

The sponsor also argues that the size of the effect attributable to ziprasidone is not clinically significant because of the absence of any clinical evidence of a risk and because of the terfenadine experience. In the ziprasidone NDA, there was no compelling evidence that sudden death was increased above background, no patients had QT prolongation at levels considered clinically significant and there were no cases of TDP. It is true that the experience with ziprasidone is in direct contrast to that with sertindole. With sertindole the effect on the QT was larger, patients had clinically significant prolongation, and the rate of sudden death appeared to be increased in both the NDA (compared to other NDAs) and in the European post-marketing experience. Pfizer also points out that terfenadine at its c max had a similar effect size and that no cases of TDP or QT prolongation have ever been found with terfenadine in the absence of a metabolic inhibitor.

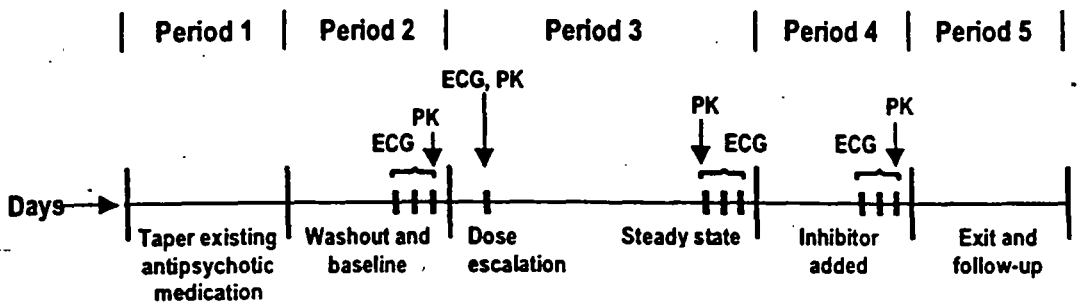
I think there are at least 2 problems with this line of reasoning. First, while the facts with terfenadine are generally correct, patient exposure to parent terfenadine is fleeting - in the order of a few minutes. So patients do not remain at risk, if there was any, for very long until terfenadine is co-administered with a metabolic inhibitor. Second, the capacity of any development program to detect an increased rate of sudden death is limited. It would have to be a large increase compared to the rates observed in other NDAs for one to reasonably conclude there was a signal of concern. Likewise, the timing of ECGs to c max may have not been sufficient to detect prolongation. TDP can be difficult to capture clinically unless investigators are looking for such events. Thus, the absence of any clinical signal in the NDA development program is not a compelling argument that they won't necessarily occur.

In short, while I agree that the clinical significance of a relatively small effect like 10 msec is not established, I don't agree that the finding is dismissible given any historical experience. I also think an even more important finding from study 054 than the experience with ziprasidone is that we can now conclude with much more certainty than in the past that risperidone, quetiapine, and olanzapine probably do not prolong the QT in their marketed dose range. This relative difference in effect between ziprasidone compared to some of the more recently approved antipsychotics raises significant need to inform investigators and patients under the ziprasidone IND about the findings from study 054.

My recommendations are (1) to include the findings from study 054 in the investigator brochure and to inform patients of these findings, in effect, conducting informed consent again for all patients exposed under the IND; (2) to ask the sponsor to try and get ECGs in patients that remain under the IND at c max and to consider discontinuing any patient with a prolonged QT; (3) to restrict any additional studies conducted under the IND to defining the level of risk from the QT effect or establishing a comparative efficacy benefit between ziprasidone and other antipsychotics, and (4) to consider withdrawing thioridazine from the market. At a minimum, I would recommend a boxed warning and reserving thioridazine for second line use.

APPEARS THIS WAY
ON ORIGINAL

A diagram showing the general study design and the timing of critical measurements is given below.



During Period 1, each subject's antipsychotic medication was tapered to the lowest possible dose over about 7 days. The investigator was to contact subjects on alternating days during this one-week period.

One day prior to the start of Period 2 (day -5), subjects entered the clinical research facility and had liver function tests performed. Results of these tests had to be reviewed before subjects were randomized to treatment assignment via tele-randomization. During Period 2, subjects received placebo once daily at approximately 0800 hours for 5 days (days –4 to 0). To standardize circadian and meal effects on QTc, the exact time of morning dosing established on day -4 was to remain fixed for the remainder of the study.

On the last 3 days of Period 2 (days -2, -1, 0), baseline ECG measurements were obtained three times daily at times specified according to treatment assignment. The times were selected so that QTc would be assessed at timepoints surrounding the mean Tmax of each agent, controlling for post-prandial time. The schedule of ECG measurements, relative to the morning dose of placebo (Period 2), antipsychotic (Period 3), and antipsychotic plus metabolic inhibitor (Period 4) is listed in Section 5.4.

During Period 3, subjects received the assigned antipsychotic drug while under continuous medical supervision in the clinical research facility. Study drug was administered in open-label fashion. The duration and dosing schedule in Period 3 were unique for each agent due to differences in tolerability, pharmacokinetics, and the time required to reach steady-state exposure. The time to achieve steady-state conditions was estimated from the average t½ of each study drug or major metabolite. For the dosing regimen used, it was anticipated that the ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol groups would reach steady-state conditions by days 8, 16, 11, 10, 8, and 10, respectively. For risperidone, olanzapine, and quetiapine, the dose escalation schedule and the Tmax were based on information provided in product labeling; for thioridazine[1,2] and haloperidol[3], the estimate of Tmax was based on literature reports. The time to achieve steady-state conditions and the Tmax for ziprasidone were based on data from previous pharmacokinetic studies that used doses from 40 to 80 mg BID.

The duration of treatment and the maximal daily dose differed across study drugs as shown below:

Table 5.1 Summary of Mean (CV%) Concentrations (ng/ml) for Parent Drug Obtained at the Time of Expected Peak Systemic Exposure
Protocol 128-054

Drug Group	Period 3 Day 2	Period 3 Low Dose*	Period 3 Steady-State	Period 4 With Inhibitor	Ratio Period 4/3
Ziprasidone	49 (41)	N/A	171 (34)	224 (35)	1.39 (40)
Risperidone	14.8 (61)	24.8 (67)	58.7 (79)	124.0 (48)	2.47 (35)
Olanzapine	9.2 (54)	N/A	55.1 (39)	84.5 (27)	1.77 (45)
Quetiapine	175 (48)	N/A	1280 (61)	3740 (43)	4.03 (70)
Thioridazine	215 (43)	N/A	765 (46)	799 (50)	1.04 (20)
Haloperidol	2.1 (91)	N/A	16.1 (95)	27.1 (75)	1.94 (50)

Source: Section 13 Tables 1.2.1 – 1.2.6

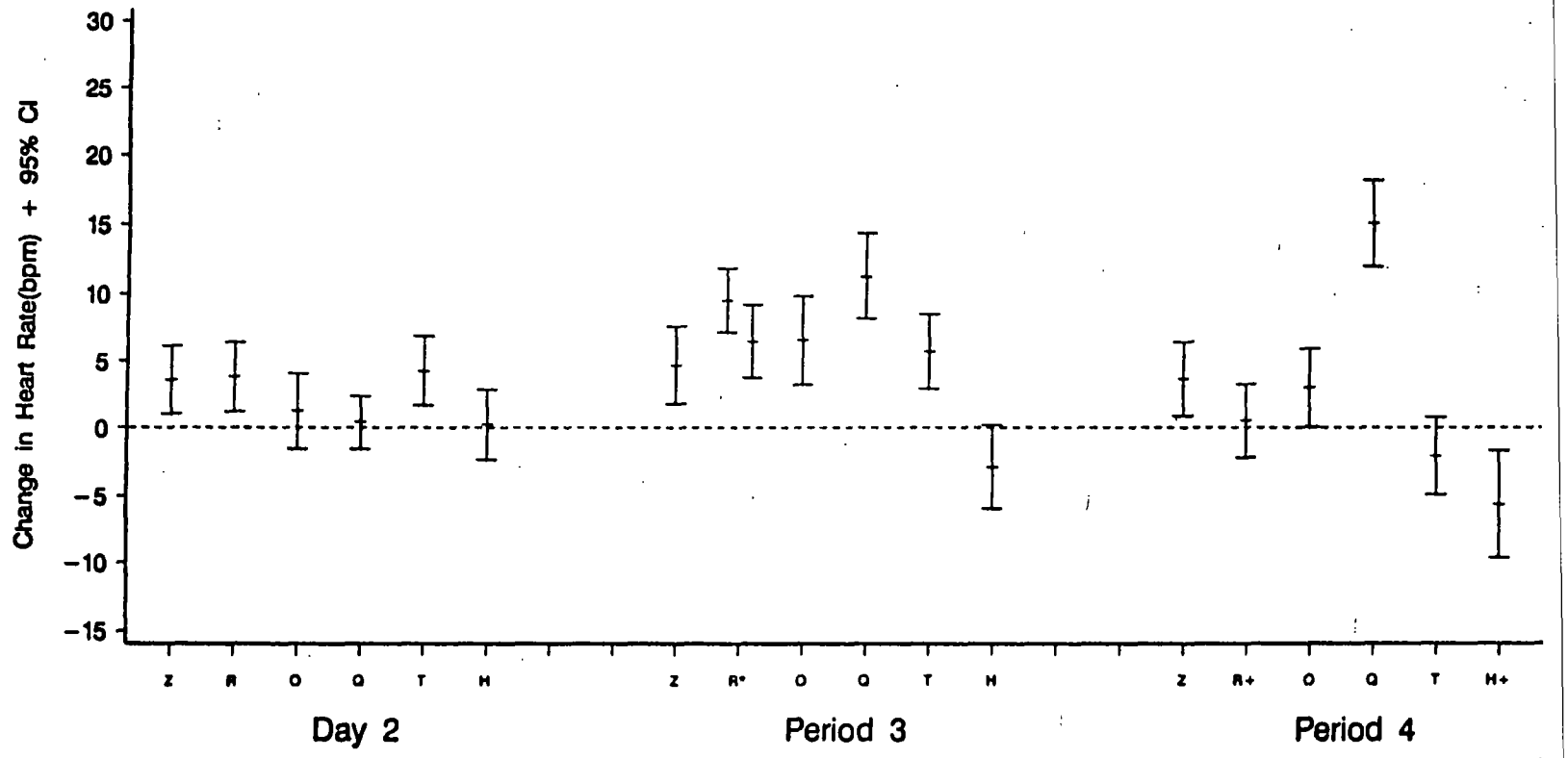
* = Applies only to the risperidone treatment group; sample obtained on day 5.

N/A = Not applicable.

Figure 2.1

Mean Change from Baseline Heart Rate(bpm) and 95% Confidence Intervals at Each Period by Treatment Group – Completers

Ziprasidone Protocol 054



Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.

* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.

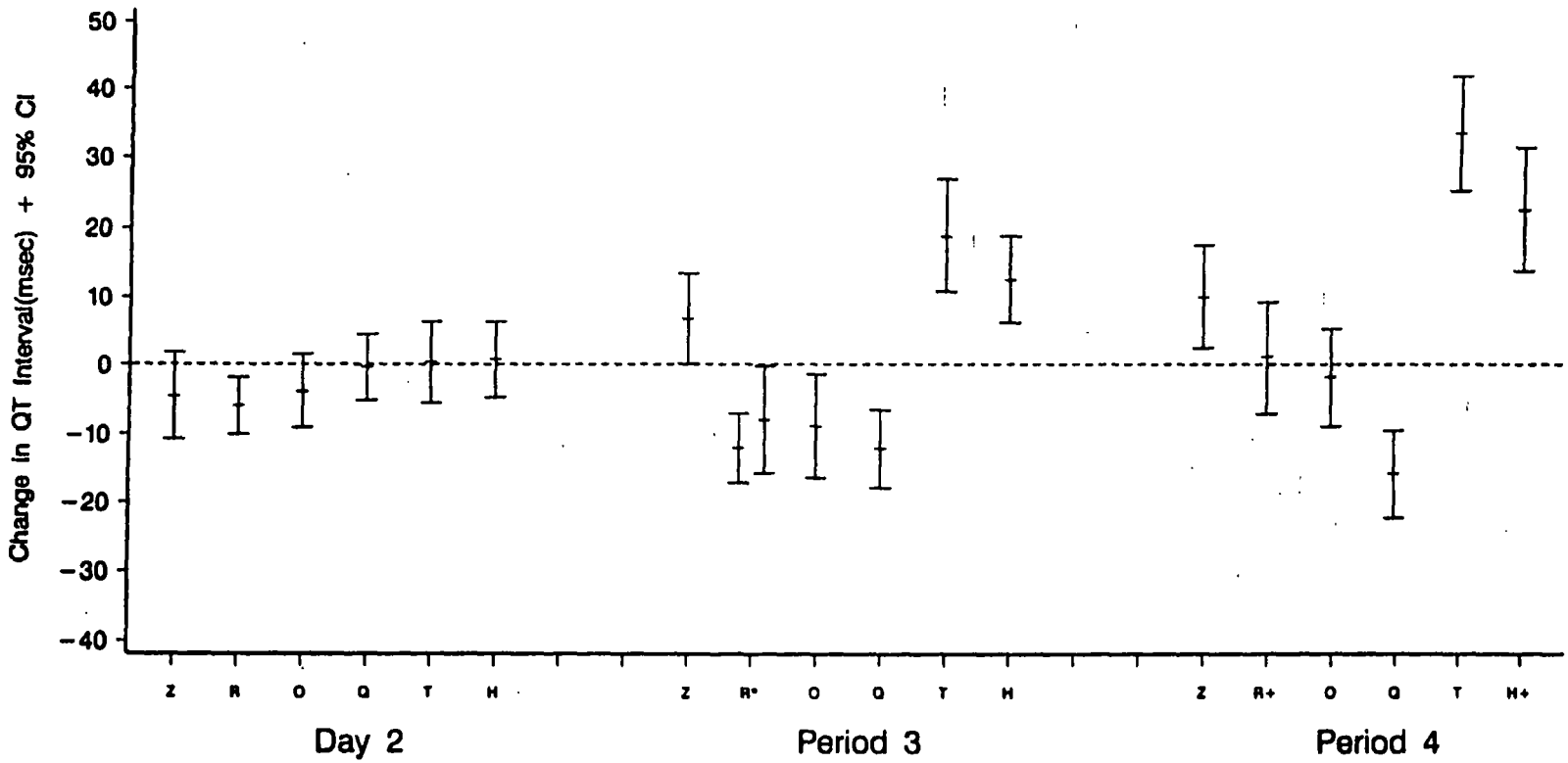
+ Contains only pre (3/16/99) amendment values, post – amendment values are provided in the listings.

Source Data: Table 5.2.2.1.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Figure 3.1

Mean Change from Baseline QT Interval(msec) and 95% Confidence Intervals at Each Period by Treatment Group – Completers

Ziprasidone Protocol 054



Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.

* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.

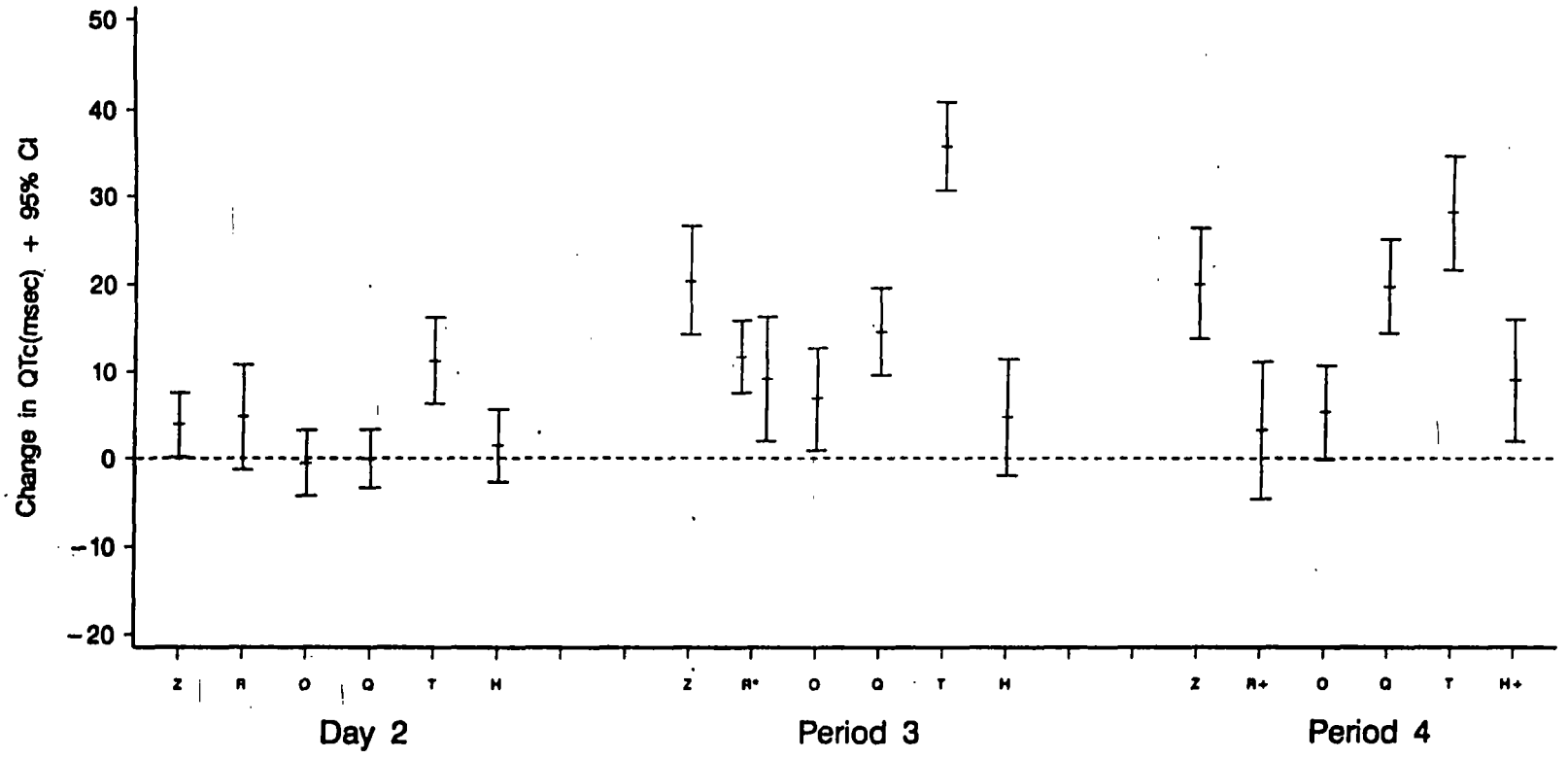
+ Contains only pre (3/16/99) amendment values, post-amendment values are provided in the listings.

Source Data: Table 5.2.3.1.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Figure 1.1.1

Mean Change from Baseline QTc Interval(msec) and 95% Confidence Intervals at Each Period by Treatment Group – Completers

Ziprasidone Protocol 054



Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.

* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.

+ Contains only pre (3/16/99) amendment values, post – amendment values are provided in the listings.

Source Data: Table 5.2.1.1.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Table 6b. QTc Change (FDA Correction (0.37 Power)) from Baseline to Last Observation; Study 054 Completers

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Baseline						
Mean (msec)	391.1	388.9	389.0	388.3	389.2	384.8
(95% CI)	(384.4, 397.8)	(382.8, 394.9)	(381.5, 396.4)	(381.3, 395.3)	(383.1, 395.3)	(378.6, 391.0)
Period 3: Steady-State (except days 5-7 for Risperidone)						
Mean Δ (msec)	16.5	4.9	2.3	6.9	30.8	6.8
(95% CI)	(11.1, 21.8)	(1.2, 8.5)	(-3.1, 7.8)	(2.9, 10.9)	(25.6, 36.1)	(1.4, 12.2)
% Δ	4.3	1.3	0.7	1.8	8.0	1.8
(95% CI)	(2.9, 5.7)	(0.3, 2.2)	(-0.8, 2.1)	(0.7, 2.8)	(6.6, 9.3)	(0.4, 3.2)
Period 3: Steady-State for Risperidone						
Mean Δ (msec)		4.3				
(95% CI)		(-2.3,10.9)				
% Δ		1.2				
(95% CI)		(-0.6, 2.9)				
Period 4: Inhibitor Present						
Mean Δ (msec)	17.0	2.7	3.3	9.5	29.3	12.8
(95% CI)	(11.0, 23.0)	(-4.6, 10.0)	(-1.7, 8.3)	(4.7, 14.3)	(23.2, 35.5)	(7.0, 18.6)
% Δ	4.5	0.7	0.9	2.5	7.6	3.4
(95% CI)	(2.9, 6.0)	(-1.2, 2.7)	(-0.4, 2.2)	(1.2, 3.7)	(6, 9.3)	(1.8, 4.9)

Source: Data on File

Table 6c. QTc Change (Framingham Linear Correction) from Baseline to Last Observation; Study 054 Completers

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Baseline						
Mean (msec)	389.4	388.2	388.4	388.1	388.5	383.7
(95% CI)	(383.5, 395.3)	(382.6, 393.9)	(381.3, 395.6)	(381.4, 394.9)	(382.6, 394.4)	(378.0, 389.3)
Period 3: Steady-State (except days 5-7 for Risperidone)						
Mean Δ (msec)	14.9	3.6	1.6	4.4	28.5	6.1
(95% CI)	(9.9, 19.8)	(-0.1, 7.3)	(-3.7, 6.8)	(0.8, 8.1)	(23.0, 34.0)	(1.0, 11.2)
% Δ	3.9	0.9	0.5	1.2	7.4	1.6
(95% CI)	(2.6, 5.2)	(0.0, 1.9)	(-0.9, 1.8)	(0.2, 2.1)	(6.0, 8.8)	(0.3, 3.0)
Period 3: Steady-State for Risperidone						
Mean Δ (msec)		3.7				
(95% CI)		(-2.2, 9.7)				
% Δ		1.0				
(95% CI)		(-0.6,2.6)				
Period 4: Inhibitor Present						
Mean Δ (msec)	15.5	2.5	2.8	5.9	28.6	12.8
(95% CI)	(9.7, 21.4)	(-4.5, 9.5)	(-2.0, 7.6)	(1.6, 10.2)	(22.2, 35.0)	(7.3, 18.2)
% Δ	4.1	0.7	0.8	1.6	7.4	3.4
(95% CI)	(2.6, 5.6)	(-1.2, 2.5)	(-0.4, 2)	(0.4, 2.7)	(5.7, 9.1)	(1.9, 4.8)

Source: Data on File

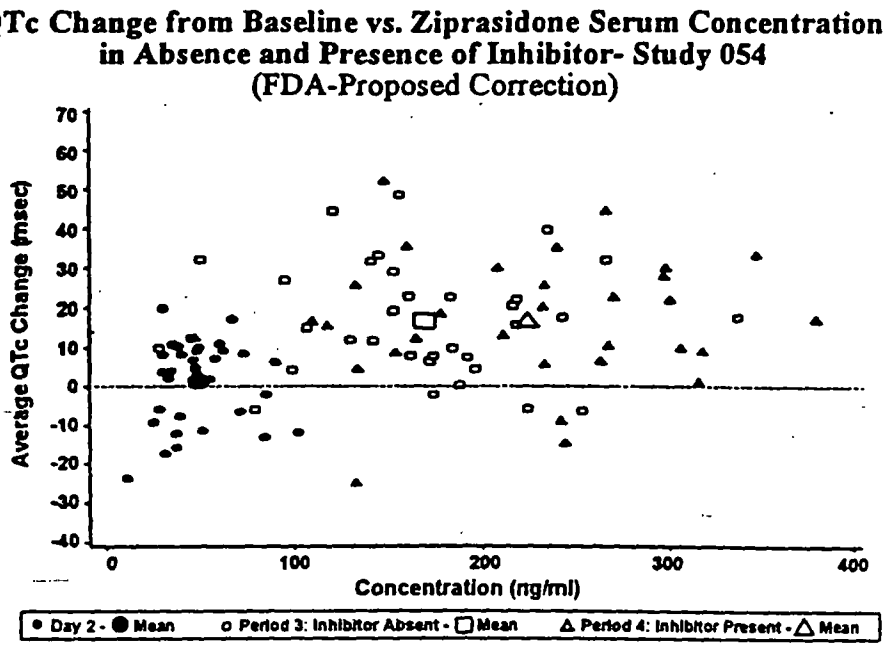


Figure 1b. Individual Mean QTc Changes (FDA-proposed Correction) from Baseline vs. Ziprasidone Serum Concentration; Study 054

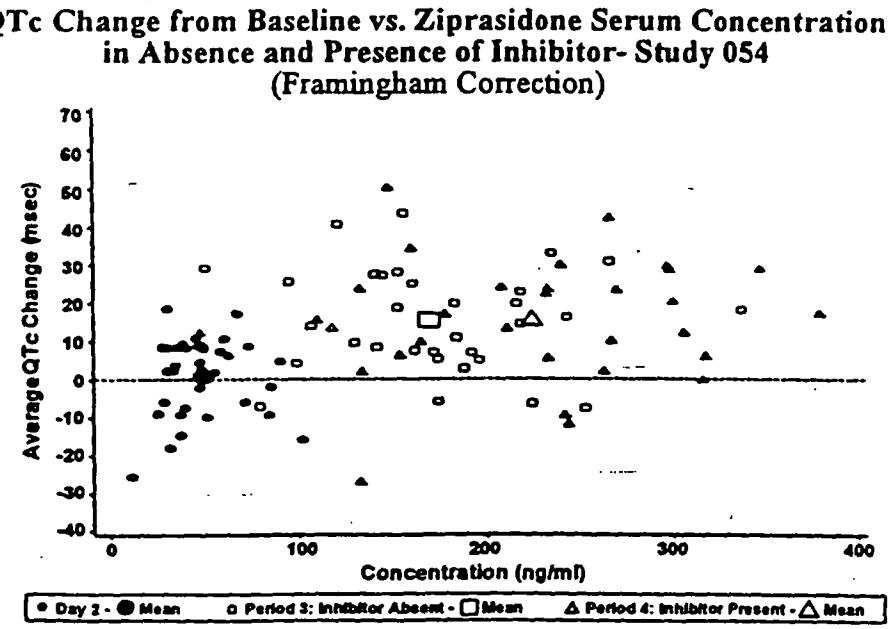


Figure 1c. Individual Mean QTc Changes (Framingham Correction) from Baseline vs. Ziprasidone Serum Concentration; Study 054

Table 5.2.3.1.1
Summary of QT Interval (msec) Baseline and Change from Baseline by Treatment Group - Completers
Ziprasidone Protocol 054

Period		Treatment Group					
		Ziprasidone	Risperidone+	Olanzapine	Quetiapine	Thioridazine	Haloperidol+
Baseline*	N	31	25	24	27	30	27
	Mean	362.2	368.9	365.0	362.4	371.3	358.7
	Std. Dev.	21.7	26.6	23.4	23.2	18.2	15.5
	Range						
	CI	(354.3, 370.2)	(358, 379.9)	(355.1, 374.9)	(353.2, 371.6)	(364.5, 378.1)	(352.6, 364.9)
Day 2	N	31	25	24	27	30	27
	Mean	-4.5	-5.9	-3.8	-0.3	0.4	0.8
	Std. Dev.	17.8	10.4	13.2	12.6	16.4	14.6
	Range						
	CI	(-11.1, 2)	(-10.2, -1.7)	(-9.3, 1.6)	(-5.3, 4.7)	(-5.7, 6.5)	(-4.9, 6.6)
Period 3#	N	31	25	24	27	30	27
	Mean	6.8	-12.1	-8.9	-12.2	18.7	12.5
	Std. Dev.	18.7	12.9	18.7	15.1	22.1	16.7
	Range						
	CI	(-0.1, 13.6)	(-17.4, -6.7)	(-16.8, -1)	(-18.2, -6.2)	(10.5, 27)	(5.9, 19.1)
Period 3^	N		25				
	Mean		-8.0				
	Std. Dev.		19.8				
	Range						
	CI		(-16.1, 0.2)				
Period 4	N	31	20	24	27	30	20
	Mean	10.0	1.1	-1.8	-15.8	33.3	22.5
	Std. Dev.	21.4	10.6	17.8	16.9	23.1	19.9
	Range						
	CI	(2.1, 17.8)	(-7.6, 9.8)	(-9.3, 5.7)	(-22.5, -9.1)	(24.7, 41.9)	(13.1, 31.8)

* Baseline is defined as the average of the planned ECGs collected on days -2, -1, and 0.
# Risperidone 6-8 mg
^ Risperidone 16 mg
+ Period 4 contains only pre (3/16/99) amendment values, post-amendment values are provided in the listings.
Source Data: Section 13 Table 18.1. Date of Data Extraction: 03JUN99. Date of Table Generation: 08JUL99.

Table 5.2.2.1.1
Summary of Heart Rate (bpm) Baseline and Change from Baseline by Treatment Group - Completers

Period		Treatment Group					
		Ziprasidone	Risperidone+	Olanzapine	Quetiapine	Thioridazine	Haloperidol+
Baseline*	N	31	25	24	27	30	27
	Mean	75.1	70.5	72.2	73.0	68.9	73.5
	Std. Dev.	12.1	11.0	8.8	7.7	8.2	10.6
	Range						
	CI	(70.7, 79.6)	(65.9, 75)	(68.5, 75.9)	(70, 76)	(65.8, 71.9)	(69.4, 77.7)
Day 2	N	31	25	24	27	30	27
	Mean	3.6	3.8	1.2	0.4	4.3	0.3
	Std. Dev.	7.2	6.6	7.0	6.2	7.3	6.8
	CI	(0.8, 6.2)	(1.1, 6.5)	(-1.7, 4.2)	(-1.6, 2.5)	(1.5, 7)	(-2.5, 3)
Period 3#	N	31	25	24	27	30	27
	Mean	4.6	9.5	6.5	11.2	5.7	-2.9
	Std. Dev.	8.2	6.0	8.2	8.2	7.7	8.2
	Range						
	CI	(1.6, 7.7)	(7, 11.9)	(3, 10)	(8, 14.5)	(2.8, 8.6)	(-6.1, 0.3)
Period 3^	N		25				
	Mean		6.4				
	Std. Dev.		6.0				
	Range						
	CI		(3.6, 9.3)				
Period 4	N	31	20	24	27	30	20
	Mean	3.6	0.5	5.0	15.1	6.1	5.7
	Std. Dev.	7.0	7.0	7.0	8.3	7.0	6.2
	Range						
	CI	(0.7, 6.5)	(-2.4, 3.4)	(-0.1, 6)	(11.8, 18.3)	(-5.1, 0.9)	(-10, -1.4)

* Baseline is defined as the average of the planned ECGs collected on days -2, -1, and 0.
\# Risperidone 6-8 mg
^ Risperidone 16 mg
\+ Period 4 contains only pre (3/16/99) amendment values. post-amendment values are provided in the listings.
Source Data: Section 13 Table 18.1. Date of Data Extraction: 03JUN99. Date of Table Generation: 08JUL99.

Review of Clinical Data

JAN 2 3 1998

Review of Ziprasidone ECG Data

NDA:	**NDA 20-825**
Sponsor:	**Pfizer**
Drug:	**Ziprasidone**
Route of Administration:	**Oral**
Reviewer:	**Gerard Boehm, M.D., M.P.H.**
Review Completion Date:	**1/23/98**

In this document, I review the sponsor's ECG data presentation included in the NDA ISS. I follow by summarizing the reviews provided by Drs. Ganley and [redacted] I then provide the results of additional analyses that I conducted using the sponsor's data from the STFDPC trials, and from study 101. I conclude with a discussion of the evidence.

NDA ISS data

Description of the collection of ECG data

There were no studies specifically designed to evaluate the effect of ziprasidone on the QTc. For the analyses presented in the NDA, the sponsor examined data recorded by 12-lead ECG's and did not identify any studies that used Holter monitors. In selected studies, investigators recorded screening, baseline, on treatment, and end of study ECG's. Investigators obtained screening ECG's during recruitment and used them to identify volunteers with ECG abnormalities for the purpose of excluding them from the study. The sponsor defined the baseline ECG as the last tracing recorded before the first day of study treatment. Depending on the protocol, these tracings could have followed a washout period where investigators discontinued the medications that subjects were taking at the time of enrollment. In some cases, the baseline ECG's were the screening ECG's (ex studies 104,106). End of study or final ECG's were the last ECG's recorded while on study treatment or within six days after the last day of study treatment. Investigators may have recorded additional ECG's during the trials (depending on the individual study protocols). With few exceptions, protocols did not specify the timing of the ECG with respect to dosing. ECG machines measured the intervals for the tracings analyzed in the ISS. The one exception was study 303, where machines read the tracings on site but the investigators also forwarded ECG's to a central site for blinded reading using an accurate, digitized methodology. The sponsor entered the ECG data into a database and calculated mean values for various parameters. The sponsor compared the mean baseline QTc to the

mean final QTc to look for evidence of prolongation. Tables in the ISS presented the data from the oral dose Phase II/III studies, the short term placebo controlled fixed dose studies (104,106,114,115), and study 303. In addition to looking for mean changes in the study population, the sponsor examined individual tracings to identify outliers (criteria: QTc≥500 or an increase in QTc≥75).

NDA Presentation of ECG Data

The NDA included the initial review of the ECG data as well as the review by Dr[ ] the sponsor's cardiology consultant.

In all oral Phase II/III trials, the final mean QTc increased from baseline for ziprasidone treated subjects (3.8) and decreased for those treated with placebo (-2.5). Similarly, in the subset of short term fixed dose placebo controlled trials, the sponsor described an increase in the final mean QTc compared to baseline in ziprasidone treated individuals (6.6), and a decrease in placebo exposed subjects (-2.6). The apparent dose response relationship presented in the following table strengthened the argument for ziprasidone's effect for prolonging the QTc.

Change from Baseline to Last Observation in QTc
Short Term Fixed Dose Placebo Controlled Trials

Treatment Group	N	Mean Change QTc from baseline
Placebo	251	-2.6
Zip<40 BID	232	4.0
Zip 40 BID	137	4.5
Zip 60 BID	111	7.3
Zip 80 BID	100	10.5
Zip≥100BID	77	12.1
Haloperidol	76	0.2

From Sponsor's table H.5.23c p.1070 Vol. 1.1

The sponsor's analysis of mean QTc difference from baseline in Study 303, a 52 week inpatient study, did not demonstrate a dose response relationship (see appendix).

The sponsor identified few ziprasidone treated patients (n=13) who met outlier criteria. The percentage of ziprasidone exposed subjects who met outlier criteria was similar to the percentage of subjects given placebo or an active comparator who met the criteria. None of the outlier ziprasidone treated patients had adverse events associated with prolonged QTc (i.e. syncope, documented arrhythmia, sudden death) and none had a prolonged QTc on more than one occasion.

The sponsor's consultant, Dr[ ]found that the ECG interval measurements were incorrect in several instances. He re-measured the intervals from some of the tracings from the STFDPC trials. Following re-measurement, he did not find a dose response relationship for QTc prolongation, but he did describe a statistically significant increase

in mean final QTc compared to baseline. Dr.[ ]felt that ziprasidone's effect on the QTc was small and not clinically significant.

An FDA cardiologist, Dr. Ganley, independently reviewed the sponsor's NDA ECG presentation as well as the ECG SAS data sets (see NDA consult dated November 18,1997). Without interval re-measurement, he found dose response relationships when analyzing all phase II/III studies and the subset of short term fixed dose studies. Dr. Ganley did not find a dose response relationship for QTc prolongation in study 303 (although he noted an increase in mean QT for the 80mg bid group accompanied by a decrease in mean heart rate which was not observed in the STFDPC trials). Dr. Ganley agreed with Dr.[ ]that the intervals were misread for many of the tracings. Despite the inconsistencies, he felt that the evidence suggested a dose response relationship for QTc prolongation and compared the change observed with ziprasidone to that seen with therapeutic doses of terfenadine. He could not estimate a risk of torsades from the data and recommended, in lieu of further clinical studies, in vitro studies of the effect of ziprasidone and its metabolites on action potential duration.

The sponsor hired Dr.[ ]to review ECG data from ziprasidone studies. He reassessed the previously identified outlier ECG tracings. Using his readings, none of these subjects had a QTc≥500 and only one met the criteria for a clinically significant change from baseline (QTc increased ≥75 over baseline). Re-measurement of intervals using the accurate, digitized methodology supported Dr.[ ]assessment.

Dr.[ ]analyzed data from study 301, and pooled data from studies 117, 108, 108E,(ongoing studies) and 303. These studies were selected because the ECG intervals had been measured using an accurate digitized methodology. He found no evidence of a dose response relationship for QTc prolongation in these data.

The sponsor then had the ECG's from the STFDPC trials re-measured using an accurate digitized methodology. After re-measurement, Dr.[ ]noted that the mean QTc difference from baseline increased with increasing ziprasidone dose for all dose groups except the ≥100mg bid group.

Change from baseline to Last Observation In QTc
Short Term Fixed Dose Placebo Controlled Trials

Treatment Group	N	Mean Change QTc from baseline
Placebo	250	-2.6
Zip<40 BID	230	0.6
Zip 40 BID	138	5.9
Zip 60 BID	111	7.7
Zip 80 BID	100	9.7
Zip≥100 BID	77	6.4
Haloperidol	76	-1.6

From Dr. , table H.5.23.2 Appendix IV

Dr. [redacted] provided an additional analysis of STFDPC trial data. He compared the ECG tracing with the largest QTc change at any time during the study with the baseline QTc. Aside from the greater magnitude of change, the results were similar to above (increasing mean QTc difference with increasing dose for all groups except the ≥100mg bid group).

When looking at the evidence in aggregate, Dr. [redacted] felt the data should be interpreted as showing no ziprasidone related dose changes. He felt that the lack of outliers argued against ziprasidone related prolongation. An additional analysis using the mean last QTc minus the mean screening QTc did not reveal a dose response relationship (contrary to what he found using the baseline QTc). He felt that if a true effect was present it should be seen regardless of the QTc used for comparison (baseline or screening). Therefore, he felt that natural variability, rather than drug effect, explained the observed changes. Additionally, the results of the analysis of study 301 did not support a dose response effect. Lastly, Dr. [redacted] presented the results of IM study 046. In this study, ziprasidone was dosed at 5 to 20mg intra-muscularly four times a day. Investigators obtained ECG's following the 4th dose on day 2. The mean QTc changes from baseline were: 5.3 for placebo; 3.5 for 20mg; 11 for 40mg; and 12.5 for 80mg. Prolongation did not appear to correlate with the estimated serum concentrations.

Re-analysis of ECG data from STFDPC Trials

Methods

Using the sponsor's data sets for the re-measured intervals from STFDPC trials, we were able to conduct our own analyses. I began by reviewing information about the individual trials to determine if it was reasonable to pool the results for analysis. Using the data sets provided, I attempted to replicate Dr. [redacted]'s findings. The sponsor included variables that identified the baseline QTc and last QTc for the patients from the STFDPC trials. I was able to reproduce the mean changes from baseline that were included with Dr. [redacted]'s results. Unfortunately, the sponsor did not include a variable that identified the QTc used in calculating the maximal QTc change from baseline. The results I obtained for this analysis are the same as Dr. [redacted]'s for all the dose groups except for <40 and 40 which differ only slightly.

During the review of the QTc prolongation issue, we became concerned about the possibility of an effect due to the timing of the last ECG tracing (up to 6 days after the last day on study medication). We hypothesized that measurement of QTc after completing treatment could reflect the return to baseline and not the effect that would be observed if the tracing were recorded while the subject was taking the drug. If this were true, the measured effect would then underestimate the actual effect of the drug. I attempted to control for this potential effect by conducting two additional analyses. After excluding any QTc value from a patient whose last ECG was recorded greater than or equal to one day after discontinuing the medication, I compared the last QTc with the

baseline QTc values. In addition, since all of these trials included a day 14 ECG, I performed an analysis comparing the day 14 QTc and the baseline QTc values.

In reviewing Dr[redacted]'s analyses, the mean QTc change values using the re-measured intervals from the STFDPC trials appeared to depict a dose response trend. We were interested in evaluating the strength of the evidence for a dose response relationship. First, we wanted to determine if the mean QTc change values were significantly different. If they were, we would perform pair wise comparisons of the mean differences. If a dose response relationship was present, and there were adequate numbers of observations, we expected that the mean QTc differences would be significantly higher in the high dose categories compared to the lower dose categories, and placebo. The STFDPC trials data was provided with the following dose groups: placebo, <40mg bid, 40mg bid, 60mg bid, 80mg bid and ≥100mg bid. These categories were used for the independent variables and the mean QTc difference from baseline was the response variable. An analysis of variance was conducted to evaluate the difference between the mean QTc change for all dosage groups. The Tukey-Kramer means comparison test was used for pair wise comparisons of the mean QTc differences for each dosage group. Regression lines were fitted using first dose group, and then estimated dose (using 12.5mg as an estimate for the categorical group <40mg and the dose in mg for the rest of the groups) by mean QTc difference from baseline. A t-test was conducted to evaluate the slope of the resulting line.

Results

The STFDPC analyses use data pooled from 4 studies. One of the potential advantages of pooling data is to increase the precision of an estimate by increasing the number of observations. Unfortunately, pooling does not result in additional observations for the 80mg bid and 100mg bid doses because all the subjects for each of these dose groups came from one study.

The STFDPC trials include four separate studies. Studies 104 and 106 were 4 weeks long and had similar entrance criteria. As mentioned above, these protocols required only a screening ECG prior to beginning the study. They both allowed the use of low dose β-blockers and lorazepam during the washout and double blind phases of the studies. Study 104 looked at the use of ziprasidone at 5mg bid, 20mg bid, and 40mg bid doses. Study 106 used 20mg bid and 60mg bid doses.

Studies 114 and 115 were similar to each other but differed slightly from the studies mentioned above. These protocols required both screening and baseline ECG's. These studies were 6 weeks in duration and both allowed the use of lorazepam, but not β-blockers, in the washout period. Both studies allowed the use of lorazepam, benztropine, or β-blockers during the double-blind phases of the studies. Study 114 used 40mg bid and 80mg bid doses while study 115 used 20mg bid, 60mg bid, and 100mg bid doses.

The following table provides the mean QTc change from baseline for the individual studies, using the mean last QTc minus the mean baseline QTc (accurate measurement methodology).

Examination of individual studies, last QTc minus baseline QTc

Study	Placebo	<40mg bid	40mg bid	60mg bid	80mg bid	>=100mg bid
104	-3.4	2.1	2.2			
106	0.1	-3.4		5		
114	-3.7		7.3		9.7	
115	-2.3	1.2		9.2		6.4

Looking at the individual study results, in all but one dosage group, the drug exposed groups had a greater mean QTc difference than the group exposed to placebo. In 2 of the 4 studies the trend was for increased effect with increased dose. The study designs and results were similar and pooling of data was considered appropriate.

The following table lists the results of the analyses using QTc values obtained at different times to calculate the mean QTc difference from baseline. The Last-baseline analysis provide the findings from Dr[ ]s analysis. The last on treatment-baseline represents the analysis which excluded patients whose last ECG was not done on the day that treatment ended. The 14 day-baseline represents the results using the mean day 14 QTc compared to the mean baseline QTc. The QTcmax-baseline represents the results of my analysis which used the maximal mean QTc difference at any time during the study compared to the mean baseline QTc (see appendix for complete tables).

Ziprasidone Short term fixed dose placebo controlled trials (104,106,114,115)

Comparison	Placebo	<40mg bid	40mg bid	60mg bid	80mg bid	100mg bid
Last-baseline	-2.6	0.6	5.9	7.7	9.7	6.4
Last on tx-baseline	-4.2	0.8	4.6	7.9	8.8	8.0
14 day- baseline	-2.6	3.4	6.1	8.4	13.3	8.5
QTcmax-baseline	4.3	9.5	12.8	15.2	19.8	15.0

Comparison of the mean QTc differences

For all of the comparisons, the mean QTc difference from baseline increased with increasing dose for all ziprasidone dose groups except for the 100mg bid group. In each of the above analyses, the results of the one way ANOVA was consistent with different means ($p<.0001$). Appendix 1 provides the pair wise comparisons for the Tukey-Kramer test. Using the mean last QTc on treatment minus baseline analysis, all dosage groups except the <40mg bid group were significantly different from placebo, but differences between mean changes for the different ziprasidone dosage groups did not achieve statistical significance. For the remaining 3 analyses, the QTc difference from baseline was also significantly higher than placebo for all dose groups except the <40mg. Additionally, the 80mg bid group was significantly higher than the <40mg bid group. The

Mean QTc difference (final on treatment from baseline) Study 101

Haloperidol	Zip 2mg bid	Zip 5mg bid	Zip 20mg bid	Zip 80mg bid
0.1(n=17)	-5.4 (n=17)	0.3 (n=17)	4.9 (n=17)	3.4 (n=19)

I repeated this analysis using the sponsors' data set that was included with the NDA submission and my results were comparable to those above. To assess the potential effect of ECG's obtained after ziprasidone was stopped, I conducted additional analyses using the day 7 (prior to am dose) and day 21 (3-7 hours after the am dose) ECG tracings.

Mean QTc difference (day 7 from baseline, day 21 from baseline) Study 101

Comparison	Haloperidol	Zip 2mg bid	Zip 5mg bid	Zip 20mg bid	Zip 80mg bid
Day 7	-6.8 (n=13)	1.4 (n=14)	6.4 (n=14)	-1.3 (n=15)	3.0 (n=17)
Day 21	-11 (n=10)	-7.6 (n=10)	5.9 (n=7)	-5.8 (n=10)	-3.0 (n=13)

I did not find a dose response relationship for QTc prolongation when comparing the mean QTc on day 7, or day 21 to the mean baseline QTc. Separate analyses looking at QT intervals by dose group also show no evidence of prolongation.

Discussion

QTc prolongation has been associated with increased mortality in healthy individuals as well as in patients with ischemic heart disease.[1,2,3,4,5] Arrhythmias and death have been associated with drugs causing QTc prolongation either alone or in combination with other agents that compete for degradation pathways.[6,7,8,9] To evaluate the potential of ziprasidone to cause QTc prolongation, the sponsor examined ECG data collected during the development program and described conflicting results. Some evidence suggests that ziprasidone causes dose dependent increases in QTc while other evidence does not support such an effect. The ability of these data to accurately describe the effect of ziprasidone on QTc is limited for several reasons.

Previous research has demonstrated that the QTc is a dynamic parameter, with demonstrated variability within individuals.[10,11,12,13] The protocol instructions for collection of ECG data in the ziprasidone NDA trials did not take this variability into consideration. For example, the baseline ECG used in these studies was a single measurement at an unspecified time (defined as the last ECG recorded prior to taking the study medication).

Timing with respect to dosing was not specified in many of the study protocols. As a result, for the on treatment tracings, some of the measurements could reflect trough concentrations, some could reflect peak concentrations, and others could reflect an intermediate concentration. Additionally, there are problems with the timing of what the sponsor defines as the last ECG. The sponsor acknowledged that some of the last ECG's were done as many as 6 days after the last dose of study drug. This disregard for timing could limit the ability to detect a drug effect, if present.

differences between the remaining groups did not achieve statistical significance.[1]

These results demonstrate that in the STFDPC trials, the difference in mean QTc from baseline was greater in the groups exposed to ziprasidone than in the groups exposed to placebo. Within the ziprasidone dosage groups, the mean QTc difference generally increases with increasing dose, but the difference achieves statistical significance only for the 80mg bid group compared to the <40mg bid group. Use of different tracings from the database for comparison appeared to have little effect on the detected mean QTc difference. The mean QTc difference was smaller for the 100mg bid group than the 80mg bid group in each of these analyses.[1]

Simple regression lines were fitted using mean last QTc and mean day 14 QTc difference from baseline by categorical dose groups and estimated dose(see appendix). The slopes of the regression lines were positive and were significantly different than zero. These findings are consistent with a dose response effect, although the models did not explain the data well with an r^2 equal to .04.[1]

Analysis of ECG data from Study 101

Methods

To further explore the possible effect of ziprasidone on the QTc, I analyzed the ECG data collected from study 101. One of the previously identified potential sources of error in the development program was the lack of protocol instructions about the timing of ECG tracings with respect to dosing. I selected Study 101 because the protocol required that ECG's be done at specified times during the trial. The study design was reviewed with emphasis on ECG data collection. I compared the mean QTc from the day 7 and day 21 tracings to the mean baseline QTc to look for prolongation.

Results

This trial was a 4 week double blinded, haloperidol controlled study in acute exacerbation of schizophrenia and schizoaffective disorder. Patients were randomized to one of 5 treatment groups (ziprasidone 2mg bid, 5mg bid, 20mg bid, 80mg bid, or haloperidol 15mg daily). Twelve lead ECG's were recorded for each subject at screening and prior to the morning dose on days 1,3,7,10,and 14. ECG's were also done 3-7 hours after dosing on days 21 and 28. The intervals were reported from the study site and were not re-analyzed using the accurate, digitized methodology mentioned previously. The QTc was derived using the following formula(
The sponsor reported the ECG results in tabular format in the study report.
The results listed in table 9.1 are summarized in the following table.

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[1]Methods and results discussed with D. Hoberman, PhD.

The sponsor concludes that ziprasidone does not cause QTc prolongation. Although there is evidence to support this conclusion (analyses of studies 108,108E,107,and 301; 303;101) because of the known variability of the QTc and the identified limitations in the methods of data collection, the ability to detect an effect, if present, is expected to be low. The sponsor dismisses the results of the STFDPC trials despite finding an increasing QTc prolongation for each increasing dose group except the highest. Additional analyses demonstrate that for all groups except the <40mg group, mean QTc difference from baseline is significantly longer than placebo. The mean QTc difference from baseline is also significantly longer for the 80mg group compared to the <40mg group. If we are to accept that there is no relationship between ziprasidone and QTc prolongation, then the sponsor must adequately explain the circumstances that led to the apparent dose response relationship findings in the STFDPC trial data.

Like much of the safety data in drug development, the ECG information was collected without intent to evaluate a specific effect. The were no studies designed to determine if ziprasidone causes QTc prolongation. The results from these analyses are only useful for generating hypotheses. The finding of SUDs rates in ziprasidone trials that are higher than observed for other recently approved antipsychotic medications, further stresses the need for additional testing to clarify the effect of ziprasidone on the QTc.

Gerard Boehm, M.D., M.P.H.
Safety Reviewer, Neuropharmacological Drug Products, HFD-120

cc:HFD-120\Boehm\Burkhart\Laughren\Leber \Glass

1-23-98
In my opinion, there is significant evidence of a "dose-response" relationship between ↑ziprasidone dose + ↑ QTinterval
It would not be surprising to see "negative" studies given the difficulty in measuring the QT.
Appropriately-powered, while carefully-designed, clinical trial could address the issue further, it is hard to believe that the dose-response relationship in the short-term fixed dose studies reviewed is a chance or bias. /S/

Appendix

Table H.5.23a
Change from Baseline to Last Observation in ECG Readings
All Oral Dosing Phase II/III Studies

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc Int (msec)	Ziprasidone	1460	409.0	408.7		412.8	412.6		3.8
	Haloperidol	281	410.3	410.5		408.7	406.7		-1.7
	Risperidone	165	409.9	407.6		407.3	407.1		-2.6
	Amisulpride	12	400.4	403.5		401.6	406.5		1.2
	Placebo	251	411.3	409.0		408.7	407.8		-2.5
QT Int (msec)	Ziprasidone	1460	364.9	364.0		366.6	364.0		1.7
	Haloperidol	281	365.0	360.0		364.6	362.0		-0.4
	Risperidone	165	367.3	365.0		363.9	362.0		-3.4
	Amisulpride	12	353.7	360.0		367.4	360.0		13.8
	Placebo	251	361.5	360.0		360.5	360.0		-1.0
Heart Rate (bpm)	Ziprasidone	1460	76.9	75.0		77.7	77.0		0.8
	Haloperidol	281	77.5	76.0		76.8	76.0		-0.7
	Risperidone	165	76.3	74.0		76.8	75.0		0.5
	Amisulpride	12	78.7	75.0		72.3	72.5		-6.3
	Placebo	251	79.3	77.0		78.9	78.0		-0.4
PR Int (msec)	Ziprasidone	1461	153.0	152.0		152.5	152.0		-0.5
	Haloperidol	283	155.4	159.0		155.4	160.0		0.0
	Risperidone	165	152.4	153.0		152.1	150.0		-0.2
	Amisulpride	12	163.4	160.0		155.5	160.0		-7.9
	Placebo	251	150.6	151.0		151.5	152.0		0.8
QRS Int (msec)	Ziprasidone	1464	85.1	84.0		84.9	84.0		-0.2
	Haloperidol	283	83.9	84.0		84.5	84.0		0.6
	Risperidone	165	84.6	83.0		85.8	85.0		1.2
	Amisulpride	12	66.7	66.5		65.9	70.0		-0.8
	Placebo	251	86.8	87.0		87.3	86.0		0.4

Protocols: 015,101,102,104,104E,106,106F,108,108E,109,109E,110,111,114,115,116B,117,118,122,301,302,304,305
*QTc Int =
Baseline = last ECG taken before the first day of study treatment.
Final = last ECG taken while on study treatment or within six days after the last day of study treatment.
Date of table generation: 10FEB97.

Table 11.5.23b
Change from Baseline to Last Observation in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change	P-Value*
**QTc Int (msec)	Ziprasidone	657	410.2	408.0		416.8	415.0		6.6	0.001
	Haloperidol	76	409.7	411.6		409.9	409.0		0.2	
	Placebo	251	411.3	409.0		408.6	407.8		-2.6	
QT Int (msec)	Ziprasidone	657	364.6	364.0		367.2	364.0		2.7	0.253
	Haloperidol	76	366.1	363.5		365.7	364.0		-0.5	
	Placebo	251	361.5	360.0		360.2	360.0		-1.3	
Heart Rate (bpm)	Ziprasidone	657	77.5	75.0		78.9	78.0		1.4	0.322
	Haloperidol	76	76.8	75.0		77.0	75.5		0.2	
	Placebo	251	79.3	77.0		79.0	78.0		-0.3	
PR Int (msec)	Ziprasidone	655	150.8	150.0		149.8	150.0		-1.0	0.171
	Haloperidol	76	152.0	152.0		153.3	156.0		1.3	
	Placebo	251	150.6	151.0		151.7	152.0		1.1	
QRS Int (msec)	Ziprasidone	657	86.3	86.0		86.1	85.0		-0.1	0.619
	Haloperidol	76	85.1	85.5		85.7	84.0		0.6	
	Placebo	251	86.8	87.0		87.3	86.0		0.4	

Protocols: 104,106,114,115
*Two-tailed T-test

Baseline = last ECG taken before the first day of study treatment.
Final = last ECG taken while on study treatment or within six days after the last day of study treatment.
Date of table generation: 10FEB97.

Table H.5.23a
Change from Baseline to Last Observation in ECG Readings
Protocol 303

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc int (msec)	20mg BID	62	409.4	407.1		411.4	409.2		2.0
	40mg BID	61	399.9	401.4		403.5	406.7		3.5
	80mg BID	59	405.6	403.0		404.8	403.7		-0.8
	Placebo	48	406.1	408.3		401.4	404.8		-4.7
QT int (msec)	20mg BID	62	364.5	365.5		363.2	355.0		-1.3
	40mg BID	61	358.5	357.0		358.9	360.0		0.4
	80mg BID	59	358.1	358.0		367.3	365.0		9.2
	Placebo	48	365.4	365.0		358.1	351.0		-7.3
Heart Rate (bpm)	20mg BID	62	77.7	74.7		79.1	78.7		1.4
	40mg BID	61	76.1	74.3		77.5	75.7		1.4
	80mg BID	59	78.5	79.7		74.5	72.7		-4.0
	Placebo	48	76.6	73.4		77.0	75.8		0.5
PR int (msec)	20mg BID	62	149.1	145.0		148.8	149.0		-0.3
	40mg BID	60	157.3	157.5		153.5	155.0		-3.8
	80mg BID	59	151.7	153.0		151.5	146.0		-0.2
	Placebo	48	148.5	150.0		145.3	145.0		-3.2
QRS int (msec)	20mg BID	62	86.0	85.0		87.7	87.0		1.6
	40mg BID	61	87.4	86.0		87.2	87.0		-0.2
	80mg BID	59	86.5	86.0		84.9	84.0		-1.6
	Placebo	48	85.2	86.5		86.5	85.0		1.3

Protocol: [redacted]
*QTc int
Baseline = last ECG taken before the first day of study treatment.
Final = last ECG taken while on study treatment or within six days after the last day of study treatment.
Date of table generation: 12MAR97.

EFFECT OF ZIPRASIDONE ON THE ECG

Objective: Purpose of the study was to determine the effect, if any, of varying doses of Ziprasidone on the ECG and to compare it with the effect of placebo and Haloperidol.

Material: The group included 658 individuals dosed with Ziprasidone, doses of 5, 20, 40, 60, 80 and 100 mg b.i.d. The N for Haloperidol and placebo was 79 and 245 respectively.

Method: The ECG variables included the heart rate, the P-R interval, QRS duration, intraventricular conduction defects, QT, QTc, ST-T, arrhythmias.

Results: There were no significant changes in heart rate, the P-R and intraventricular conduction after administration of Ziprasidone.

A statistically significant change at a p level of 0.05 or less was noted in the duration of the QT when compared with placebo at doses of 80 and 100 mg. The absolute prolongation was in the order of nsec respectively. No statistically significant change was noted at doses of 5, 20, 40 and 60 mg. The absolute difference between baseline and final mean for the 80 and 100 mg dose was 7.8 and 8.2 msec respectively.

A statistically significant prolongation of QTc, when compared with placebo, at a level of 0.05 or less, was noted at doses of 20, 40, 60, 80 and 100 mg. However, the respective absolute prolongation was No statistically significant change was noted at 5 mg dose. The absolute difference between the baseline and final mean for the 5 doses was 5.9, 3.6, 5.8, 10.6 and 8.4 msec respectively. In no instance did the QTc exceed 490 msec.

Conversion from normal to abnormal was observed in 37 (5.6%) of the 658 dosed individuals. Similarly, 39 (5.9%) converted from abnormal to normal during therapy. Of the 324 Haloperidol and placebo 15 (4.9%) converted from normal base to abnormal and 25 (7.7%) from abnormal to normal. The most frequent change was from normal ST-T to abnormal ST-T. Isolated prolongation of the P-R, QRS, appearance of LVH, LAFB, and rare PVCs were also noted.

Comment: As indicated there was no physiologically or statistically significant change in heart rate, P-R and QRS intervals. The ST-T changes most frequently noted are common, reflecting the very labile nature of repolarization (ST-T) and, thus, expected over the period of the trial. Furthermore, similar changes from abnormal ST-T to normal were observed. Similar incidence of conversion from normal to abnormal ST-T was recorded in the placebo group. Furthermore, the abnormalities did not appear dose related.

The isolated prolongation of the P-R, QRS, the LVH and the rare PVC are rarely if ever due to drugs.

Although there was some statistically significant prolongation of the QTc after dosing, and when compared with placebo and Haloperidol, the absolute prolongation was small and clinically insignificant.

Summary: There was no clinically significant effect of Ziprasidone on the ECG.

/S/

M.D.

Table H.5.23.2 (Pooled) - Centrally Read 108,108E,117, & 303
Change from Baseline to All Post Baseline Values in ECG Readings
By Actual Study Drug Dose Taken the Day of the Reading
Centrally Read Maintenance Oral Dosing Phase II/III Studies

	Zip <20mg BID			Zip 20-<40mg BID			Zip 40-<60mg BID			Zip 60-<80mg BID			Zip 80-<100mg BID		
	N	Base Mean	Mean**	N	Base Mean	Mean**	N	Base Mean	Mean**	N	Base Mean	Mean**	N	Base Mean	Mean**
*QTc int	234	405.1	0.3	172	406.8	2.8	309	407.0	3.0	71	410.0	-0.6	165	408.0	1.7
QT int	234	364.7	-2.5	173	368.3	0.6	309	366.3	3.5	70	371.1	2.1	165	366.3	9.6
Heart Rate	234	75.7	1.5	173	74.8	1.0	309	75.5	-0.2	70	74.9	-1.1	165	76.0	-3.2
PR int	233	153.9	-1.4	173	152.3	-1.2	306	155.8	-1.9	70	154.4	-0.7	165	151.7	-1.3
QRS int	234	86.1	-0.1	173	85.7	-0.7	309	85.5	-0.1	70	83.1	-0.8	165	84.6	0.1

(CONTINUED)
Protocols: 108,108F,117,303
*QTc int
** Mean change from baseline to subject baseline value using all post baseline readings.
Total Changed = number of postbaseline ECG values within six days after the last day of study treatment for which that dose level of study drug was taken the day of the ECG readings.
Date of table generation: 21OCT97.

Results of the reanalysis of ECG data from the STFDPC trials

Last minus baseline

	n	mean QTc baseline	mean QTc last	QTc difference	QT difference	pulse difference
Placebo	250	399	396.5	-2.6	0.3	-1.1
<40 mg	230	396.9	397.5	0.6	-4.4	2.4
40 mg	138	397.6	403.4	5.9	0.3	2.2
60 mg	111	398	405.7	7.7	7.1	-0.2
80 mg	100	394.6	404.3	9.7	7.2	0.4
>=100 mg	77	402.7	409.1	6.4	5.8	0.2

Last on treatment minus baseline

	n	mean QTc baseline	mean last QTc	QTc difference	QT difference	pulse difference
Placebo	152	399.8	395.6	-4.2	0.2	-1.4
<40 mg	147	397.1	397.8	0.8	-2.7	1.7
40 mg	78	398.6	403.1	4.6	1.8	1.1
60 mg	74	398.1	405.9	7.9	8.8	-0.9
80 mg	57	394.7	403.4	8.8	6	0.8
>=100 mg	52	403.1	411.1	8	7.9	-0.3

Day 14 minus baseline

	n	mean baseline QTc	mean d14 QTc	QTc difference	QT difference	pulse difference
Placebo	197	399.7	397.1	-2.6	0	-1.1
<40 mg	179	386.4	399.7	3.4	-5.9	4.1
40 mg	116	397.7	403.8	6.1	-1.2	3.3
60 mg	97	398.8	407.2	8.4	6.3	0.2
80 mg	92	395.7	409	13.3	4.1	3.2
>=100 mg	69	402	410.5	8.5	10.1	-0.8

QTc max minus baseline

	n	mean baseline QTc	mean max QTc	QTc difference	QT difference	pulse difference
Placebo	250	399	403.4	4.3	-1	2.2
<40 mg	230	396.9	406.4	9.5	-5.2	6.1
40 mg	138	397.6	410.4	12.8	0.6	4.6
60 mg	111	398	413.2	15.2	5.7	3
80 mg	100	394.6	414.4	19.8	6.2	4.6
>=100 mg	77	402.7	417.7	15	9.7	1.8

Tukey Kramer Pair wise comparison of the mean QTc differences

Using last on treatment minus baseline

	Placebo	<40	40	60	80	100
Placebo		-	+	+	+	+
<40	-		-	-	-	-
40	+	-		-	-	-
60	+	-	-		-	-
80	+	-	-	-		-
100	+	-	-	-	-	

+Significant difference

Using Last minus baseline

	Placebo	<40	40	60	80	100
Placebo		-	+	+	+	+
<40	-		-	-	+	-
40	+	-		-	-	-
60	+	-	-		-	-
80	+	+	-	-		-
100	+	-	-	-	-	

+Significant difference

Using Day 14 QTc-baseline

	Placebo	<40	40	60	80	100
Placebo		-	+	+	+	+
<40	-		-	-	+	-
40	+	-		-	-	-
60	+	-	-		-	-
80	+	+	-	-		-
100	+	-	-	-	-	

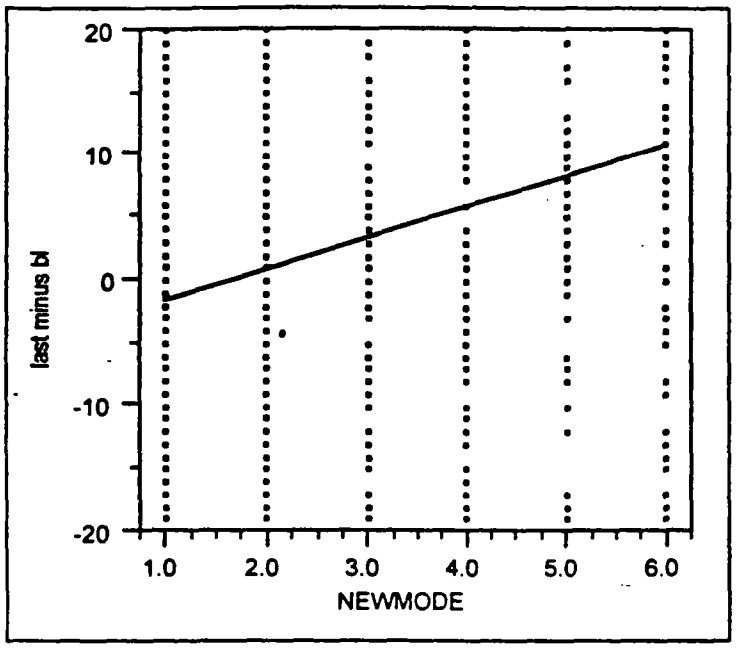
+Significant difference

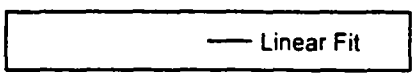
Using QTcmax minus baseline

	Placebo	<40	40	60	80	100
Placebo		-	+	+	+	+
<40	-		-	-	+	-
40	+	-		-	-	-
60	+	-	-		-	-
80	+	+	-	-		-
100	+	-	-	-	-	

+Significant difference

last minus bl By NEWMODE





Linear Fit

last minus bl = -4.0292 + 2.48476 NEWMODE

Summary of Fit

RSquare	0.038618
RSquare Adj	0.037555
Root Mean Square Error	20.17928
Mean of Response	2.909492
Observations (or Sum Wgts)	906

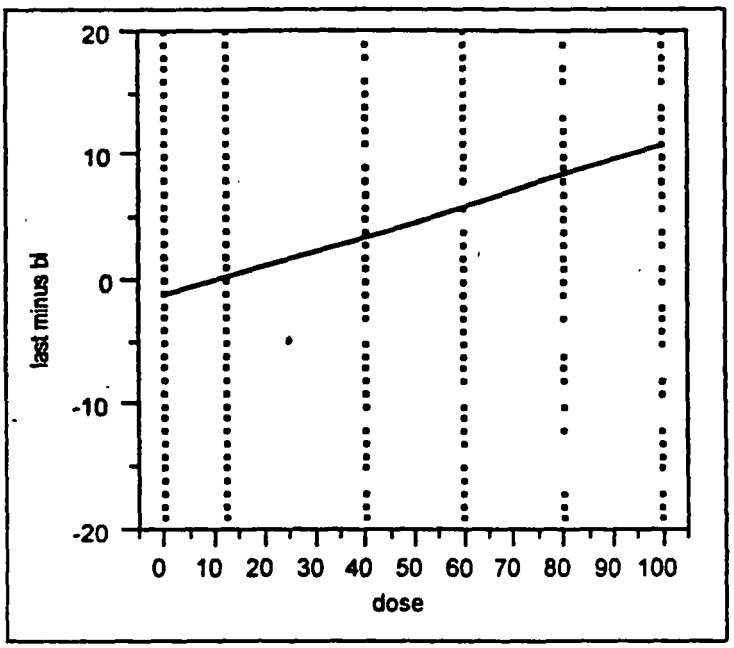
Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	14786.80	14786.8	36.3131
Error	904	368111.78	407.2	Prob>F
C Total	905	382898.58		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-4.0292	1.332402	-3.02	0.0026
NEWMODE	2.4847649	0.412338	6.03	<.0001

last minus bl By dose



Linear Fit

Linear Fit

last minus bl = -1.1723 + 0.12024 dose

Summary of Fit

RSquare	0.038604
RSquare Adj	0.03754
Root Mean Square Error	20.17943
Mean of Response	2.909492
Observations (or Sum Wgts)	906

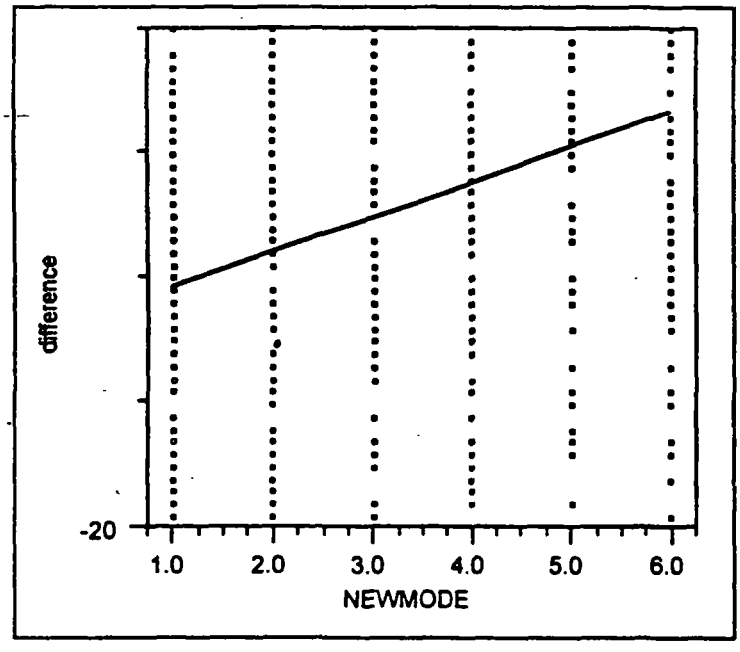
Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	14781.35	14781.4	36.2991
Error	904	368117.23	407.2	Prob>F
C Total	905	382898.58		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-1.172281	0.953125	-1.23	0.2190
dose	0.1202434	0.019958	6.02	<.0001

difference By NEWMODE



— Linear Fit

Linear Fit

difference = -3.6359 + 2.83924 NEWMODE

Summary of Fit

RSquare	0.049201
RSquare Adj	0.047929
Root Mean Square Error	20.62923
Mean of Response	4.56
Observations (or Sum Wgts)	750

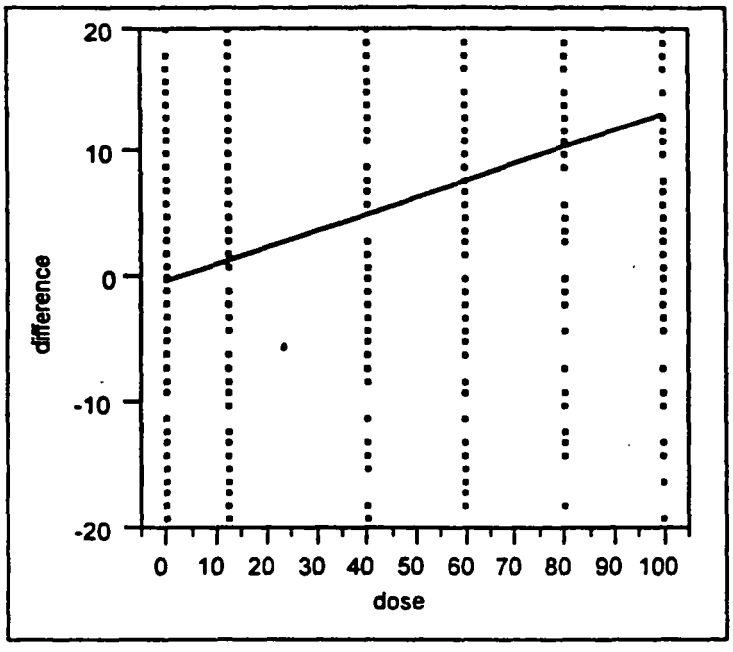
Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	16472.11	16472.1	38.7064
Error	748	318322.69	425.6	Prob>F
C Total	749	334794.80		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-3.635928	1.517522	-2.40	0.0168
NEWMODE	2.8392359	0.456362	6.22	<.0001

difference By dose



Linear Fit

Linear Fit

difference = -0.2855 + 0.13481 dose

Summary of Fit

RSquare	0.047369
RSquare Adj	0.046095
Root Mean Square Error	20.64909
Mean of Response	4.56
Observations (or Sum Wgts)	750

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	15858.89	15858.9	37.1938
Error	748	318935.91	426.4	Prob>F
C Total	749	334794.80		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-0.285523	1.095343	-0.26	0.7944
dose	0.13481	0.022105	6.10	<.0001

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APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

Food and Drug Administration
Center for Drug Evaluation and Research
Division of CardioRenal Drug Products
Consultation

Date: 6/14/00

To: Russell Katz, MD
Division Director, HFD-120

From: Maryann Gordon, MD /S/
Medical Reviewer, HFD-110

Through: Shaw Chen, MD. PhD /S/
Medical Team Leader, HFD-110

Dr. Raymond Lipicky /S/
Division Director, HFD-110

Subject: Ziprasidone, NDA# 20825
Study report of Clinical Pharmacology Protocol #128-054

Conclusion

Study 128-054 has demonstrated that the antipsychotic agents ziprasidone and thioridazine adversely affect cardiac repolarization in that these drugs prolong the QTc and QT intervals in a concentration-related manner. Patients who take drugs that prolong these ECG intervals are at risk of serious cardiac arrhythmias such as torsade de points (TdP) and sudden death. The effect on cardiac repolarization of the other antipsychotic agents used in study 128-054 for comparison appears to be minimal or absent.

Taking into account ECG data from this study as well as other trials, ziprasidone increases the QTc from baseline on average about 10-20 msec, thioridazine approximately 36 msec, and sertindole, an antipsychotic removed from the UK market for causing TdP and sudden death, about 21 msec. Although the magnitude of the increase of the QTc (and QT) is thought by experts to be important, it is not predictive of the degree of risk of TdP or other serious ventricular arrhythmias.

The co-administration of a metabolic inhibitor with ziprasidone and thioridazine increased blood levels and QTc only slightly compared to the use of these drugs alone. Therefore, drug-drug interactions similar to what occurred with terfenadine (when blood levels increased dramatically when ketoconazole was taken along with terfenadine) are much less of a concern with these agents.

In summary, a certain proportion of patients taking ziprasidone or thioridazine will have an increased risk of potentially fatal ventricular arrhythmias. The Cardio-Renal Division considers it essential that any agent with an added safety risk, unless efficacy data suggest superior benefit compared to other drugs for the same indication, should either not be made available or should be reserved for second line therapy.

Finally, adverse effects such as increases in total cholesterol and large weight gains reported with some of the other antipsychotic agents are unlike sudden death in that they can be identified early and the patient at risk can be switched to another agent. Therefore, the claim that ziprasidone has less cardiovascular risk factors because the drug causes less weight gain and/or improves lipid profile cannot offset its likely

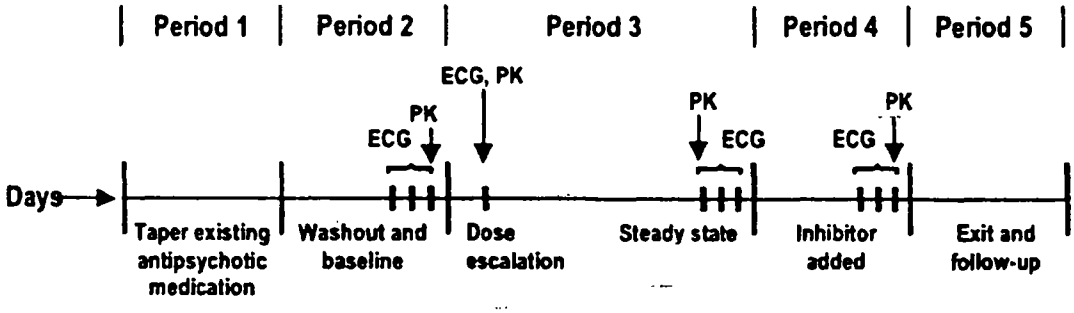
propensity to cause sudden death.

Introduction
(Please refer to previous consults written by Dr. C. Ganley and dated 12/17/98, 11/18/97, and 2/21/97)

The sponsor of ziprasidone was sent a letter by the Agency on 6-17-98 stating that the drug was not approvable because of its effect on cardiac repolarization. The concern was that the "modest" effect (QTc[1] prolongation of about 10 msec with the 160 mg dose) was an underestimation because the ECGs were not obtained at maximum drug concentration. The study reviewed here was specifically designed to address this issue and also to compare the effect of ziprasidone on cardiac repolarization to the effect of other approved antipsychotic drugs.

Study Design, protocol #128-054
This was a randomized, open-label, parallel, multi-center study in subjects with normal ECGs (QTc <450 msec) and psychotic disorders. Following a screening phase, the trial consisted of five different treatment periods:
Period 1: subjects who were eligible for enrolling in the study had their current medication tapered over several days as an out-patient;
Period 2: subjects entered a clinical research facility to be completely withdrawn from current therapy.
Period 3: subjects were randomized to one of six treatments (ziprasidone, risperidone, olanzapine, quetiapine, thioridazine or haloperidol) with the dose escalated over 10 to 19 days;
Period 4: after the maximum dose of randomized therapy was achieved, the metabolic inhibitor selected for each drug was administered;
Period 5: after steady state is reached with the combination of randomized therapy and a metabolic inhibitor, the subjects were withdrawn from therapy.

The study diagram is shown below.



ECGs were obtained at baseline, at start of study drug (day 2), at steady state (period 3), and with the inhibitor (period 4). ECGs were recorded at times estimated to correspond with the mean Tmax for each study drug.

Dosing and metabolic inhibitors

Subjects were to be titrated to the highest dose tolerated. The initial and maximum doses used for each

[1] Bazett's correction: QTc=QT/sqrt (60/hr rate)

treatment group and the doses of the metabolic inhibitors are shown below.

Study Drugs (Period 3)	Potency (mg)	Initial Dose (mg/day)	Maximum Dose (mg/day)
Ziprasidone	20, 40, and 80 (capsules)	40	160
Risperidone	1, 2, 3, and 4 (tablets)	2	16
Olanzapine	5 and 10 (tablets)	5	20
Quetiapine	25, 100, and 200 (tablets)	50	750
Thioridazine	25 and 100 (tablets)	50	300
Haloperidol	2, 5, and 10 (tablets)	2	15
Metabolic Inhibitors (Period 4)			
Paroxetine	20 (tablet)	20	
Ketoconazole	200 (tablet)	400	
Fluvoxamine	50 (tablet)	50	100

There were changes with the administration of the inhibitors during period 4:
Originally,
-ketoconazole (200 mg BID) was administered with ziprasidone and quetiapine,
-paroxetine (20 mg 00) was administered with thioridazine and risperidone,
-fluvoxamine (50 mg escalating to 100 mg QD) was administered with olanzapine.
-paroxetine (20 mg QD) and ketoconazole (200 mg BID) were administered with haloperidol.

Late in the study, ketoconazole (200 mg BID) was substituted for paroxetine as the metabolic inhibitor in the risperidone group, and the regimen for dosing ketoconazole to the haloperidol group was changed from 200 mg BID to 400 mg QD by protocol amendment.

Comments on the protocol raised by Dr. Ganley
1) the study was to enroll a sufficient number of subjects such that 150 subjects (25 per group) completed the entire study. There was no explanation in the protocol to justify the sample size.
2) The protocol was lacking in its description of how the QTc data should be interpreted. There was, however, an expectation that the change in QTc interval with ziprasidone therapy was to be different from haloperidol.

Study results

A total of 183 subjects were randomized and had evaluable ECG data. Patient demographics are shown below.

	Baseline Demographic Characteristics											
	Ziprasidone		Risperidone		Olanzapine		Quetiapine		Thioridazine		Haloperidol	
	M[a]	F[b]	M	F	M	F	M	F	M	F	M	F
Number of subjects	25	10	22	6	20	8	22	7	25	6	25	7
Mean age (yrs)	38.6	36.1	38.3	37.3	38.2	38.6	38.1	40.6	35.5	37.3	33.7	43.0
Age range (yrs)	22-58	20-47	20-55	29-47	22-58	25-53	26-47	27-57	21-48	30-44	20-47	35-49
Mean weight (kg)	85.9	79.8	84.1	88.0	86.0	86.2	83.9	87.7	90.5	87.1	77.9	75.6

[a]M=male; [b]F=female

Mean age and range, mean weight and number of subjects were reasonably similar for the different treatment groups.

There were 8 subjects (2 ziprasidone, 3 quetiapine, and 3 haloperidol who did not reach the protocol-specified maximum daily dose of study drug in Period 3. Seven of the eight were discontinued prematurely. The eighth received 600 mg of quetiapine at steady-state rather than 750 mg because of adverse events. This subject completed the study. One thioridazine subject required a dose higher than that specified in the protocol.

Heart rate and correction factors

QT interval is inversely related to heart rate (normally, the slower the heart rate the longer the QT interval). To compensate for normal variations in heart rate, the Bazett's correction, known as QTc, is used. The use of Bazett's correction factor is controversial with drugs that increase heart rate. Among the group of drugs studied here, quetiapine was the only one that consistently raised heart rate throughout the study. The mean change from baseline heart rate for the various agents are shown in the attachment.

QT/QTc

Baseline is defined as the average of the planned ECGs collected on days –2, -1, and 0.
All ECGs were obtained at Tmax and all were read centrally. QTc intervals were provided by the central reader.

Mean changes
The tables below show the mean change QTc and QT from baseline at the start of titration (day 2) and at steady state (period 3).

Start of titration

Mean change (SD) from baseline at Day 2: msec

	Zisprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QTc	3.0 (10.7)	4.7 (14.1)	0.3 (9.0)	-0.5 (8.6)	11.2 (13.2)	2.2 (12.4)
QT	-3.6 (17.3)	-5.3 (11.2)	-3.7 (12.8)	-0.1 (12.4)	1.1 (16.6)	-0.8 (15.6)

Tables 5.2.2.1 and 5.2.3.2.1

At the start of dosing, only thioridazine shows a substantial prolongation of the QTc (11.2 msec). Changes from baseline in QTc/QT are similar for ziprasidone and the rest of the agents.

Steady state

Mean change (SD) from baseline at Period 3: msec

	Zisprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QTc	20.6 (16.4)	10.0 (11.1)	6.4 (13.6)	14.5 (12.7)	35.8 (13.5)	4.7 (16.9)
QT	7.0 (18.40)	-11.8 (12.8)	-9.3 (18.0)	-12.2 (15.1)	19.7 (22.3)	12.5 (16.7)

Tables 5.2.2.1 and 5.2.3.2.1

Thioridazine at steady state caused a 35.8 msec increase in QTc (9% increase from baseline) and a 19.7 msec increase in QT (5% increase from baseline). The next largest increase was caused by ziprasidone with a 20.6 msec increase in QTc (5% increase from baseline) and a 7 msec increase in QT (2% increase from baseline). While risperidone, olanzapine, and quetiapine were associated with an increased QTc, the QT was decreased for these agents. Haloperidol increased QTc by 4.7 msec and it is generally accepted, perhaps erroneously, that its effect on QTc is not different from placebo.

With metabolic inhibitor

Mean change (SD) from baseline at Period 4: msec

	Zisprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Ratio^	1.39	2.47	1.77	4.03	1.04	1.94
QTc	20.4 (17.0)	3.2 (16.9)	5.3 (12.8)	19.7 (13.5)	28.0 (17.3)	8.9 (15.0)
QT	9.9 (21.0)	1.1 (18.6)	-1.8 (17.8)	-15.8 (16.9)	33.3 (23.1)	22.5 (19.9)

^drug concentrations period 4: period 3

Tables 5.2.2.1, 5.2.3.2.1, and page 38 of study report

Quetiapine showed the largest increase in plasma concentration when subjects were also given a metabolic inhibitor. Compared to steady state, the concentration of ziprasidone increased slightly while the mean QT/ QTc prolongation (20.4/9.9 msec) was basically unchanged.

Outliers

The tables below shows the number and percent of subjects with QTc increases from baseline of $\geq$ 30, $\geq$ 60, and $\geq$ 75 msec for the various drugs at steady state (period 3) and with the metabolic inhibitor (period 4).

Number and (percent) of subjects Period 3

Increase from baseline	Zisprasidone N=33	Risperidone 16 mg N=28	Olanzapine N=26	Quetiapine N=27	Thioridazine N=30	Haloperidol N=20
QTc: $\geq$ 30 msec	21 (64)	12 (46)	9 (35)	14 (52)	30 (97)	11 (41)
QTc: $\geq$ 60 msec	7 (21)	1 (4)	1 (4)	3 (11)	9 (29)	1 (4)
QTc: $\geq$ 75 msec	1 (3)	0	0	0	3 (10)	0

Table 5.3.3.2

Number and (percent of subjects) Period 4

Increase from baseline	Zisprasidone N=32	Risperidone N=20	Olanzapine N=24	Quetiapine N=27	Thioridazine N=30	Haloperidol N=20
QTc: $\geq$ 30 msec	25 (78)	8 (40)	8 (33)	8 (67)	27 (90)	9 (45)
QTc: $\geq$ 60 msec	4 (13)	0	0	4 (15)	6 (20)	0
QTc: $\geq$ 75 msec	1 (3)	0	0	0	4 (13)	0

Table 5.3.4.2

Only thioridazine and ziprasidone increased QTc by 75 msec or more in at least 1 study patient.

Relationship to drug concentration.

The attached figures[2] show individual QTc and QT values plotted against drug concentration on a log scale for each of the antipsychotic agents. The steepness of the slope indicates the magnitude of increase in QTc and QT for every log increase in concentration.

Thioridazine and ziprasidone showed the steepest slope for both QTc and QT followed by haloperidol. While the effect of quetiapine on the QTc was impressive (slope of 15), the changes in QT was negative. Olanazepine had a small positive slope and the slope for risperidone was flat.

Lipid profiles

Median changes and median percent changes from baseline at last planned visit prior to discharge in fasting serum cholesterol and triglycerides are shown below by treatment group.

Serum Lipid Concentrations: Median Baseline (Median Change; mg/dl) and % Change from Baseline

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Cholesterol						
Total	197.5(-14.5^{c})	204.0(-3.0^{a})	201.0(4.0^{i})	196.0(5.0^{i})	186.0(21.0^{c,i})	193.0(-22.0^{c})
% Change	-7.5^{b}	-1.6^{a}	2.1^{i}	2.4^{i}	13.7^{c,i}	-11.5^{c}
HDL	43.5(0.0)	41.0(-2.0)	44.0(-2.0)	45.0(-3.0)	41.0(1.5)	43.0(-3.0^{b})
% Change	0.0	-4.9	-4.6	-8.6	3.0	-6.0^{a}
LDL	122.0(-11.0)	125.0(9.0^{a})	128.0(1.5)	117.0(-0.5^{a})	121.0(20.0^{c,i})	121.0(-14.0^{c})
% Change	-8.5	6.5^{a}	1.1	-0.3^{a}	18.6^{c,i}	-10.5^{c}
Triglycerides	141.0(-37.0^{c})	158.0(-17.0)	148.0(43.0^{c,i})	124.0(25.0^{c,i})	120.0(9.0^{a})	118.0(-18.0^{b})
% Change	-28.0^{c}	-6.7^{a}	31.0^{c,i}	18.3^{c,i}	7.9^{i}	-18.0^{b}
Total/HDL Ratio	4.31(-0.33^{b})	5.43 (0.31^{a})	5.14(0.28^{a})	4.42(0.48^{a,i})	4.61(0.41^{a,i})	4.26(-0.22^{a})
% Change	-7.5^{b}	5.9^{A,a}	5.4^{A,a}	10.8^{a,i}	12.4^{c,i}	-7.0^{A}

^{A}p<0.05; ^{b}p<0.01; ^{c}p<0.001 versus baseline using Wilcoxon signed rank test on change from baseline values against 0;
^{a}p<0.05, ^{b}p<0.01, ^{i}p<0.001 versus ziprasidone by two-sided Wilcoxon test.

The sponsor claims that ziprasidone has a beneficial effect on lipid profiles. In the Division's opinion, if patients need control of their lipids, treating them with a lipid lowering agent would be preferred.

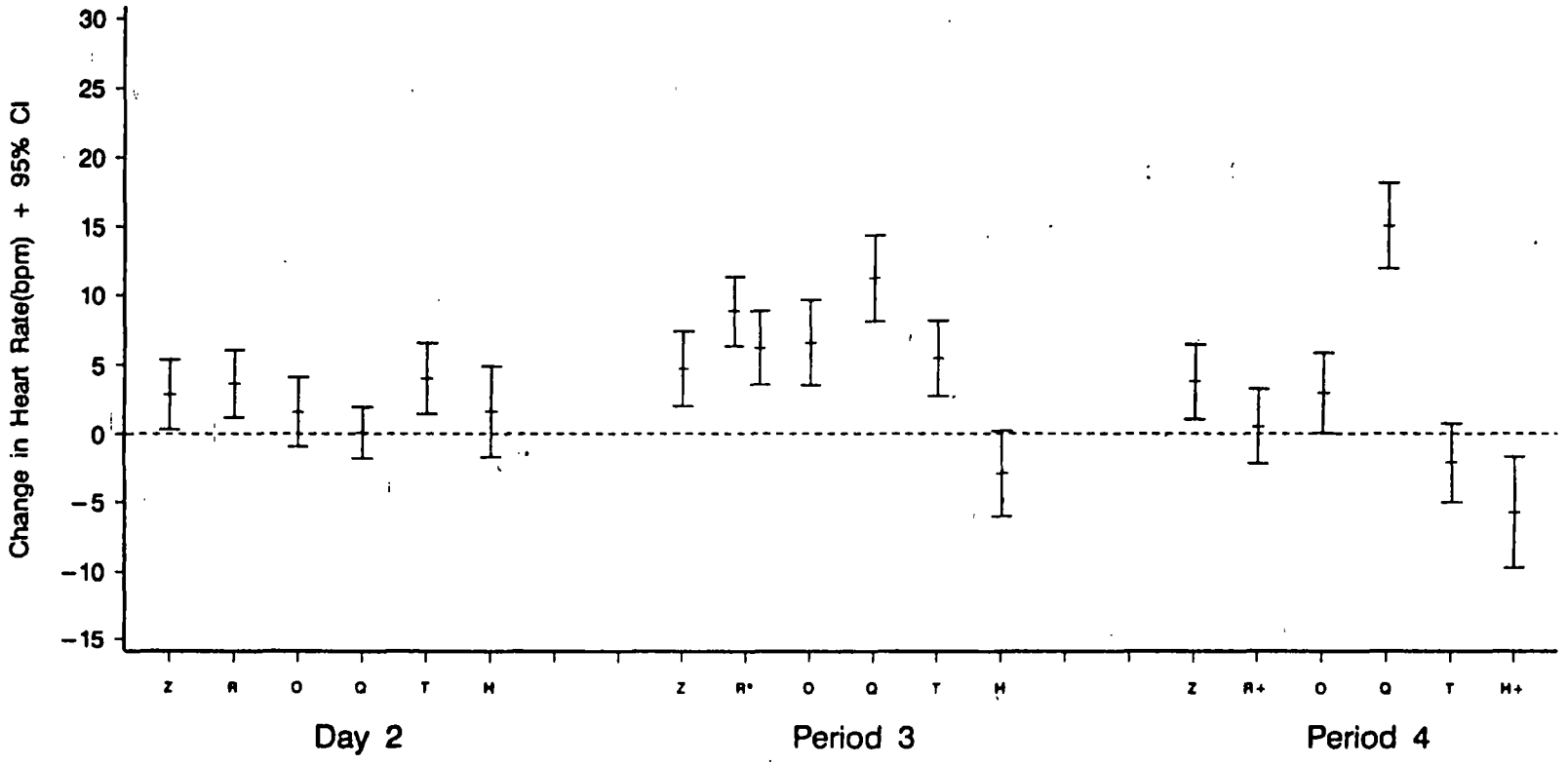
cc /S/
Orig.
HFD-110/SChen
HFD-120/RGlass/TLaughren

[2] courtesy of Dr. Gabriel Robbe, Biopharmacology Reviewer

Figure 2.2

Mean Change from Baseline Heart Rate(bpm) and 95% Confidence Intervals at Each Period by Treatment Group – All Subjects

Ziprasidone Protocol 054



Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.

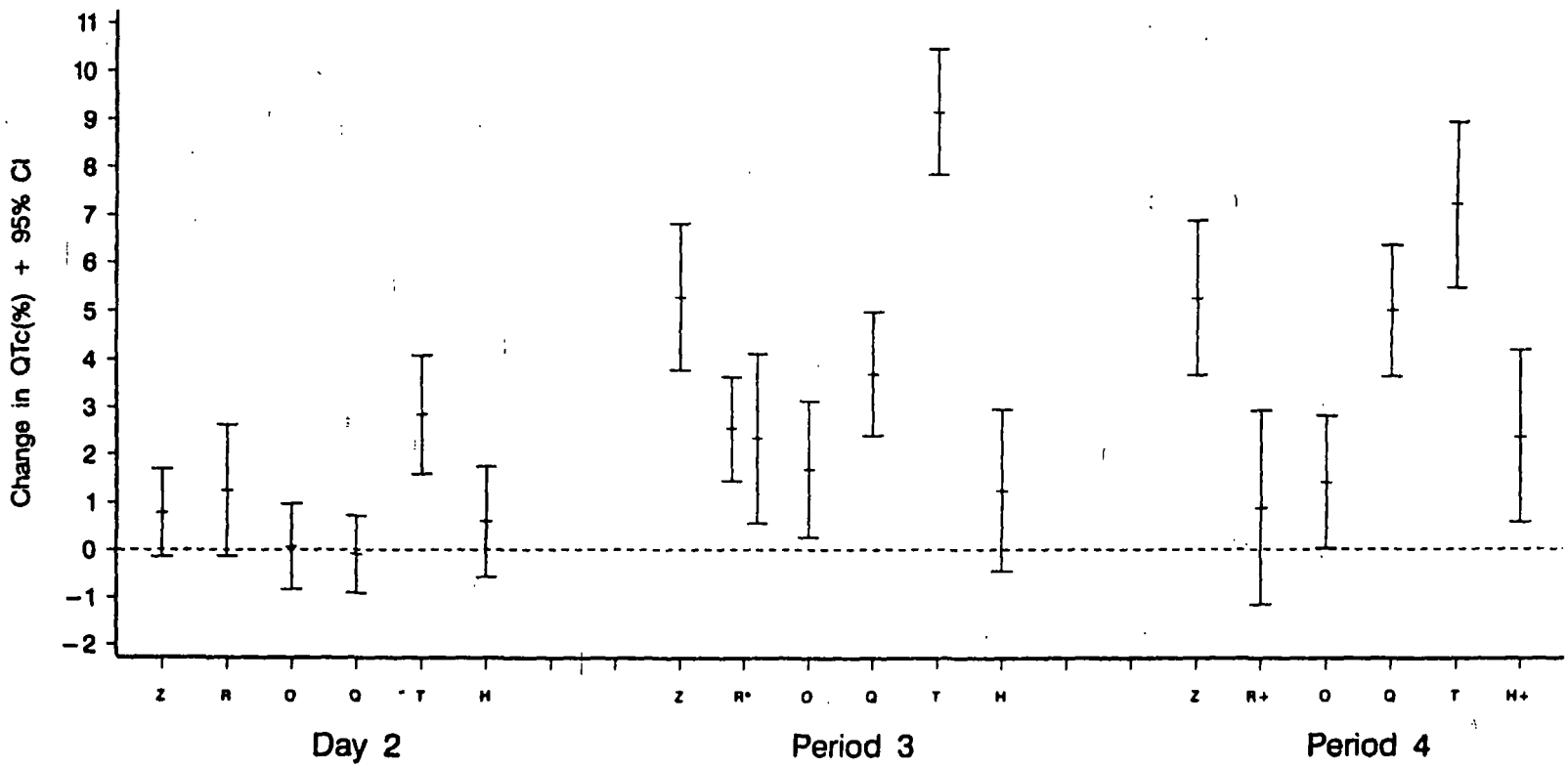
* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.

+ Contains only pre (3/16/99) amendment values, post – amendment values are provided in the listings.

Source Data: Table 5.2.2.2.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Figure 1.2.2

Percent Change from Baseline QTc Interval(msec) and 95% Confidence Intervals at Each Period by Treatment Group – All Subjects
Ziprasidone Protocol 054

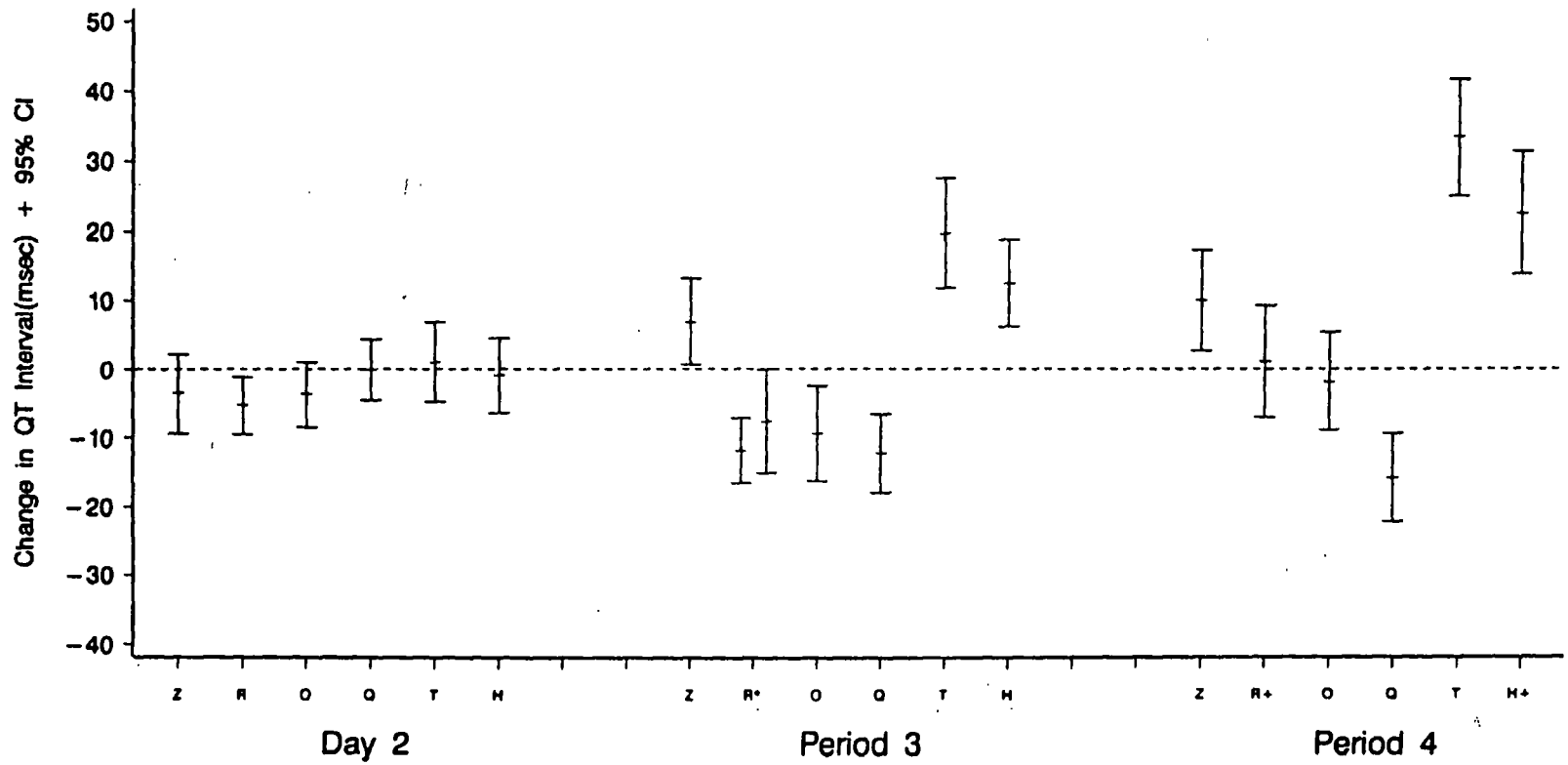


Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.
* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.
+ Contains only pre (3/16/99) amendment values, post – amendment values are provided in the listings.
Source Data: Table 5.2.1.2.2. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Figure 3.2

Mean Change from Baseline QT Interval(msec) and 95% Confidence Intervals at Each Period by Treatment Group – All Subjects

Ziprasidone Protocol 054



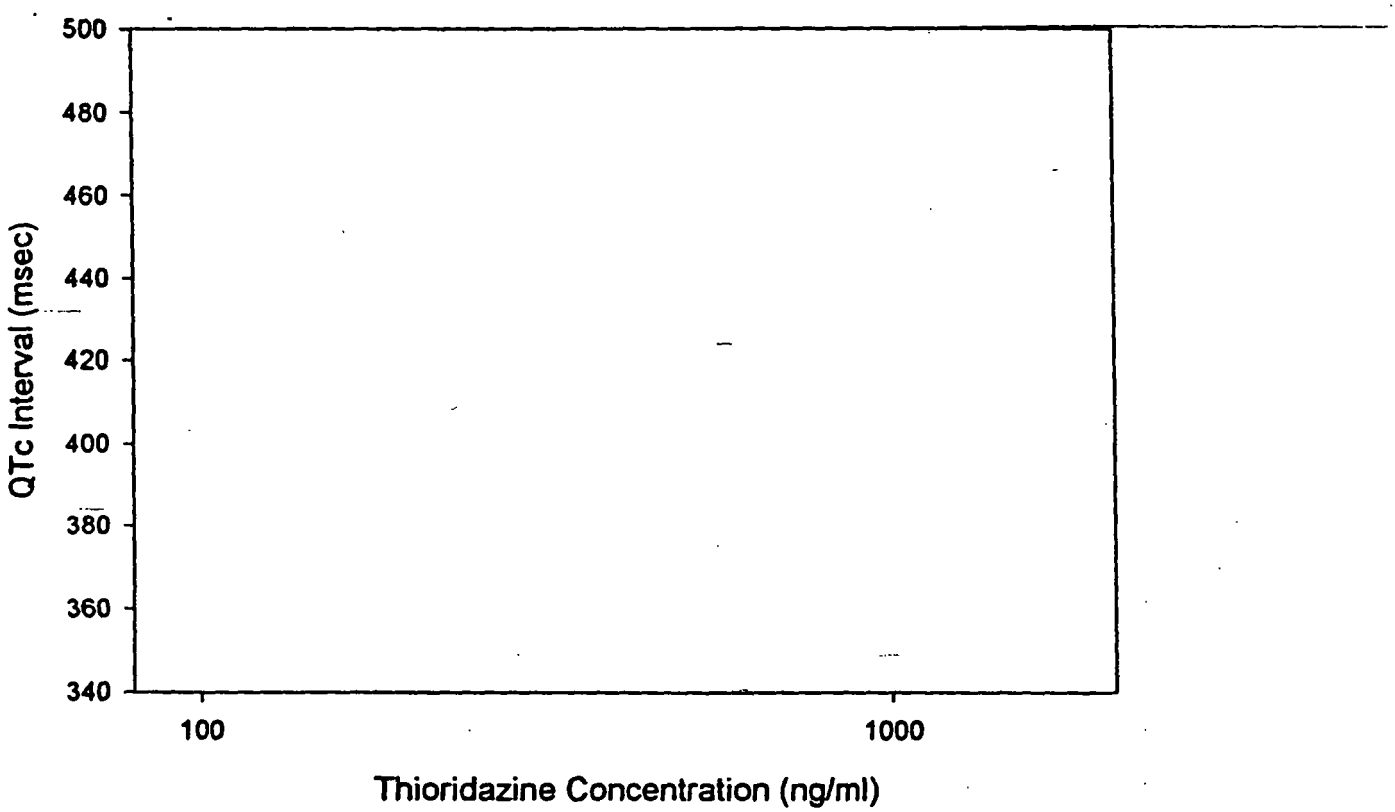
Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.

* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.

+ Contains only pre (3/16/99) amendment values, post – amendment values are provided in the listings.

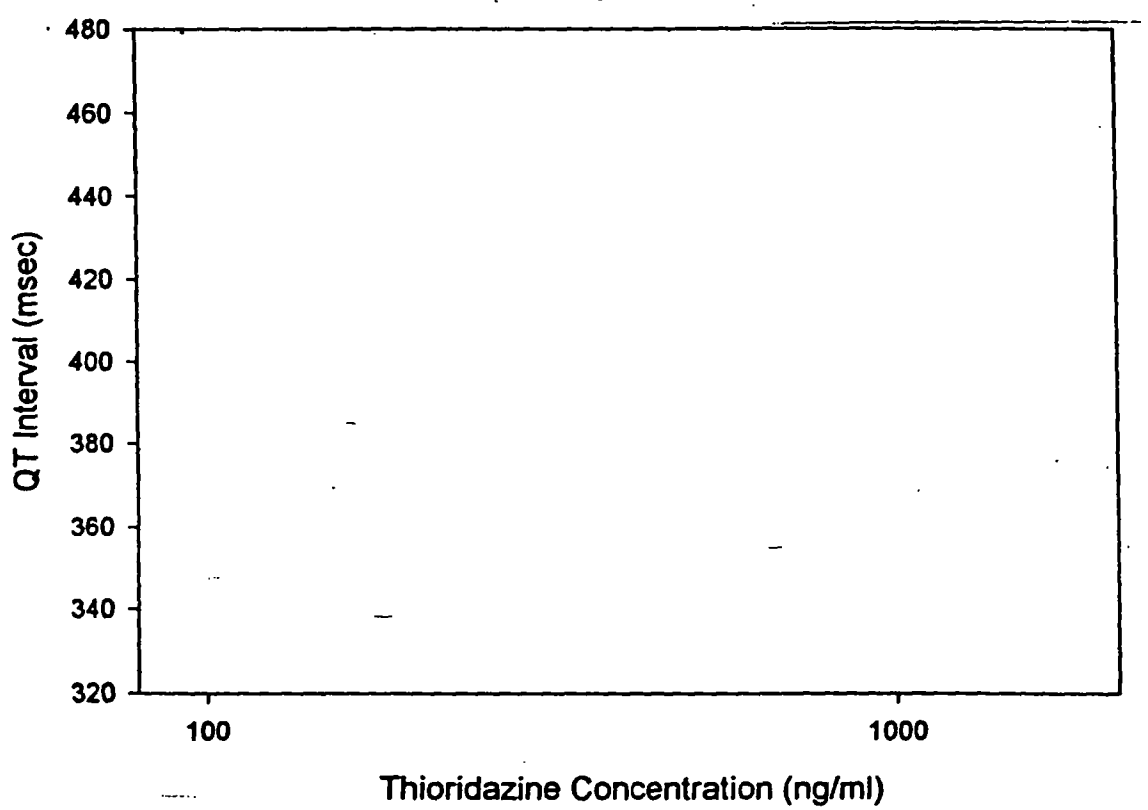
Source Data: Table 5.2.3.2.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Effect of Thioridazine on QTc Interval



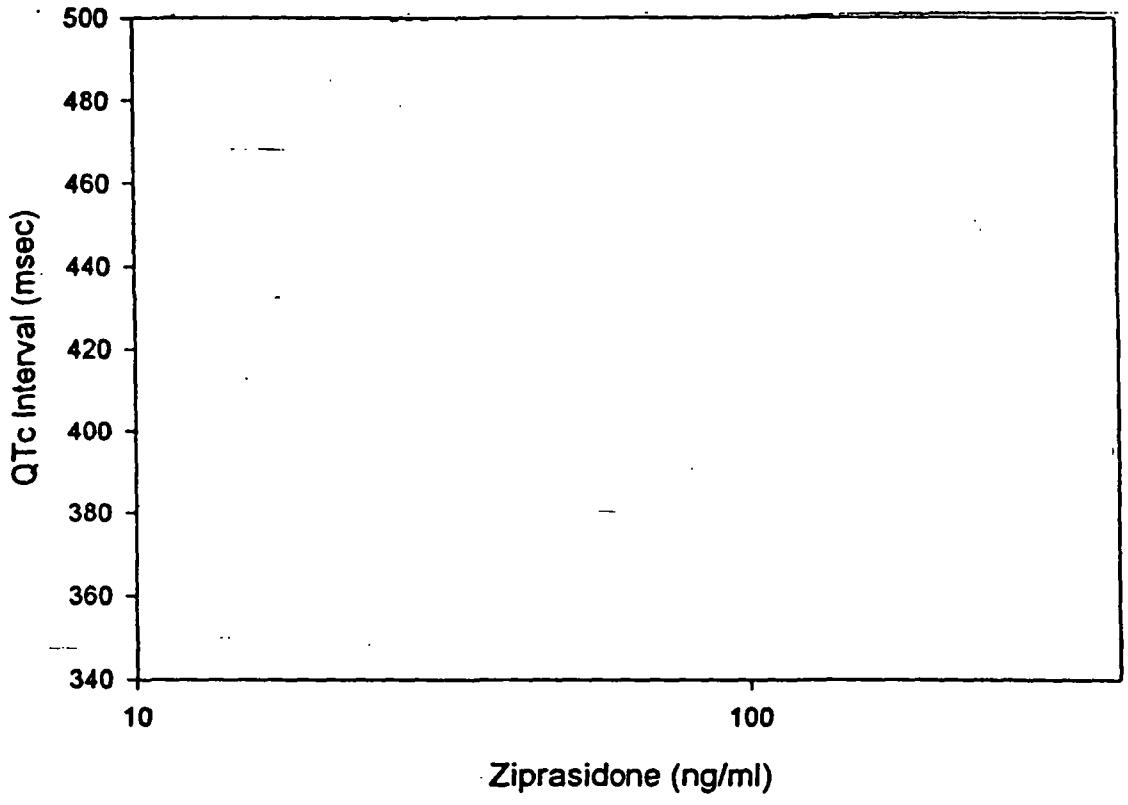
Intercept = 311.7693
Slope = 40.4152
r^2=0.248075

Effect of Thioridazine on QT Interval



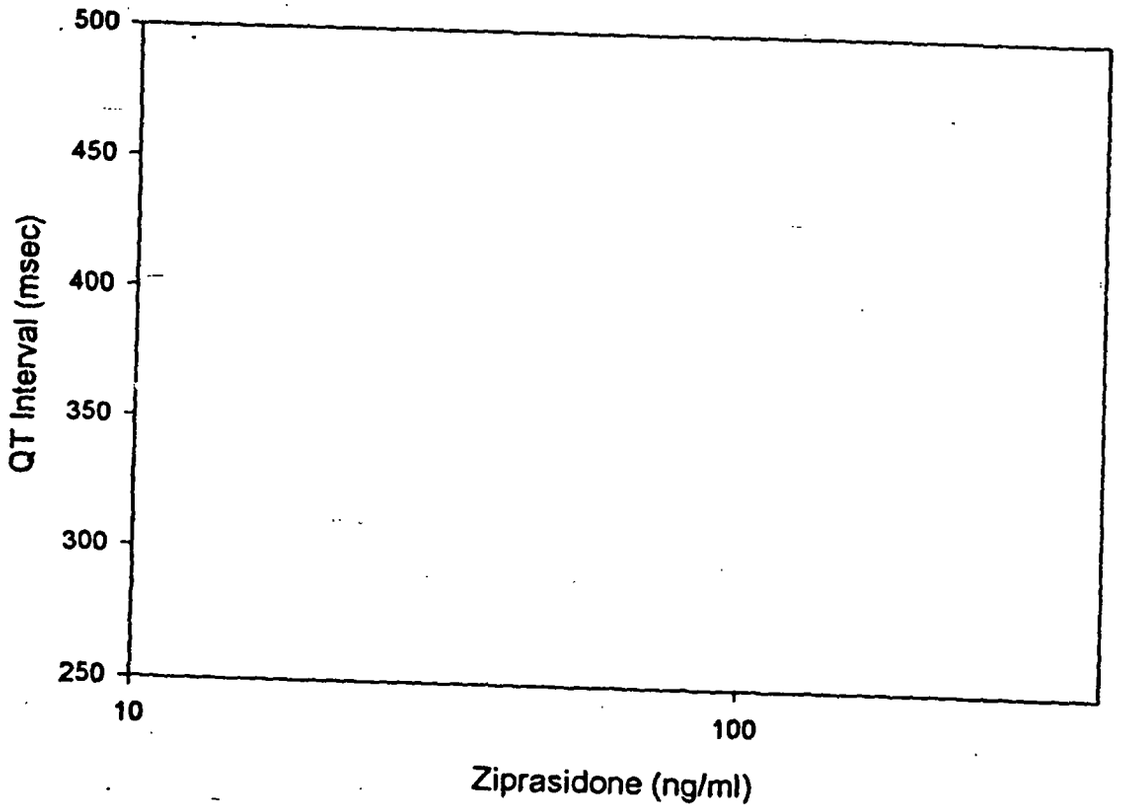
Intercept = 272.776
Slope = 44.17474
r^2=0.2164634033

Effect of Ziprasidone on QTc Interval



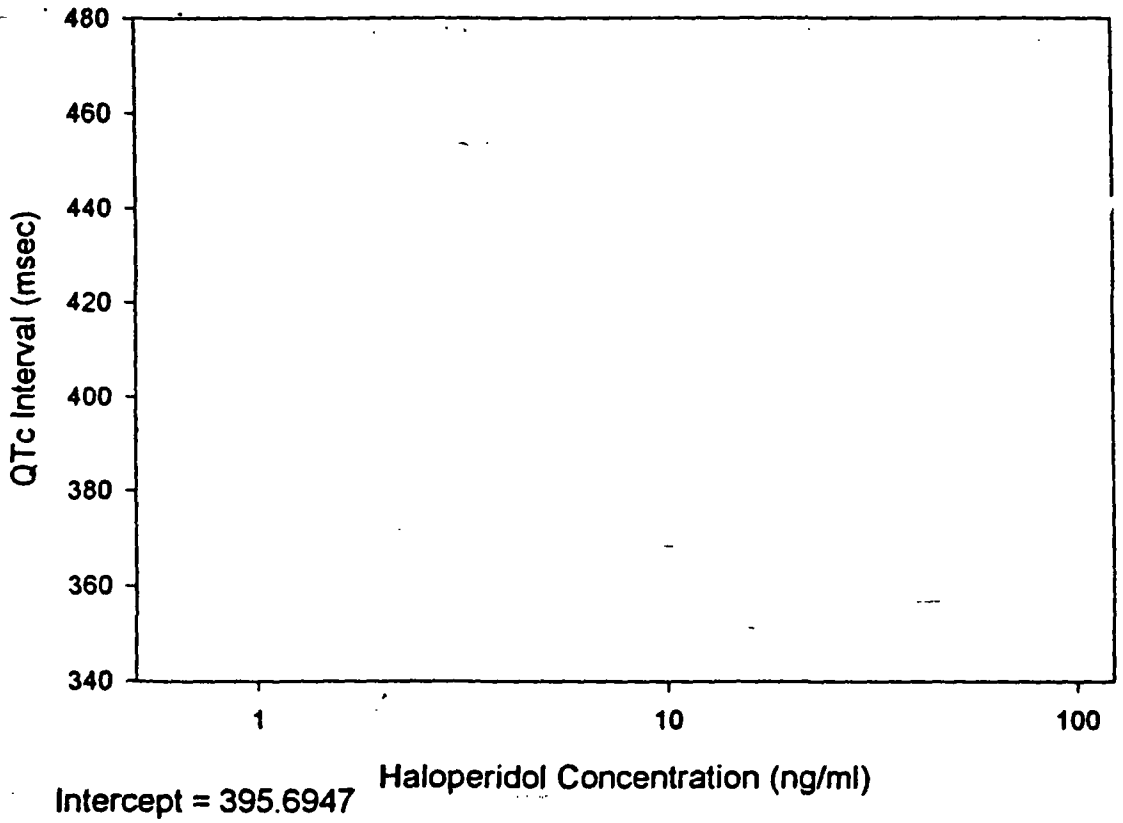
Intercept = 372.711
Slope = 21.57282
r2 = 0.09080

Effect of Ziprasidone on QT Interval



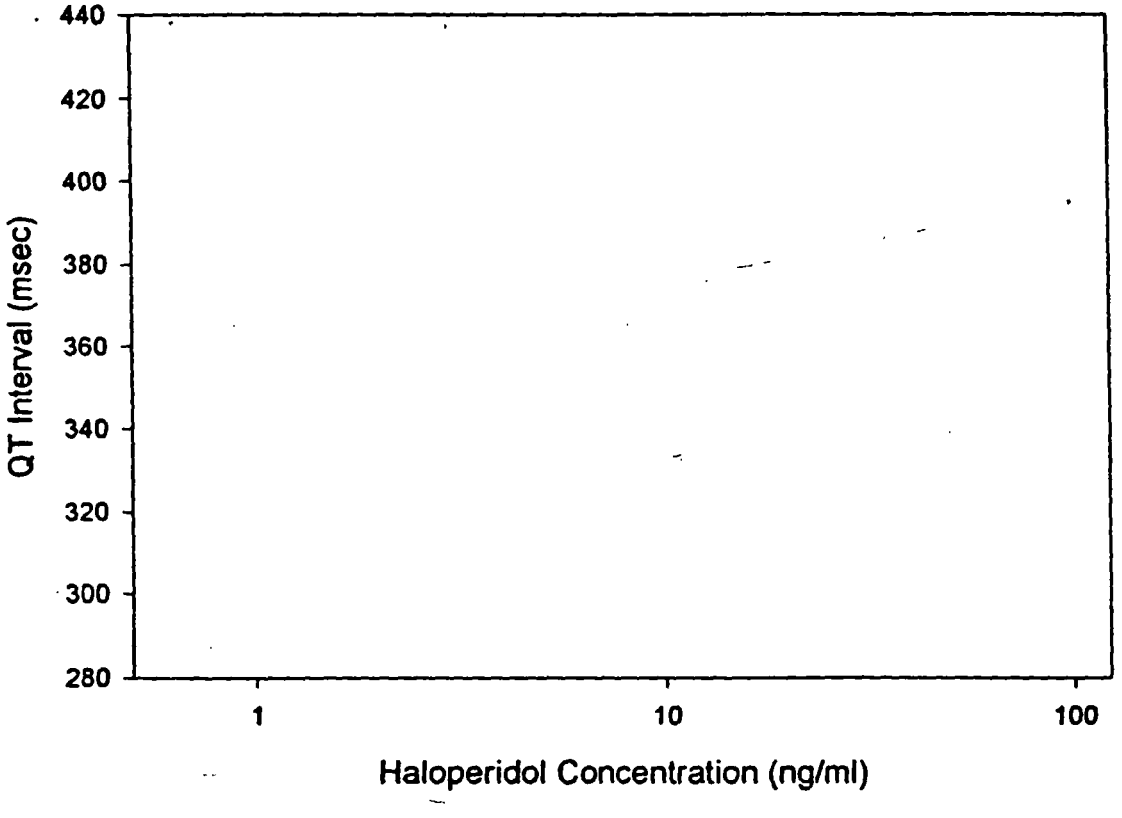
Intercept = 319.724
Slope = 23.342
r^2= 0.082985

Effect of Haloperidol on QTc Interval



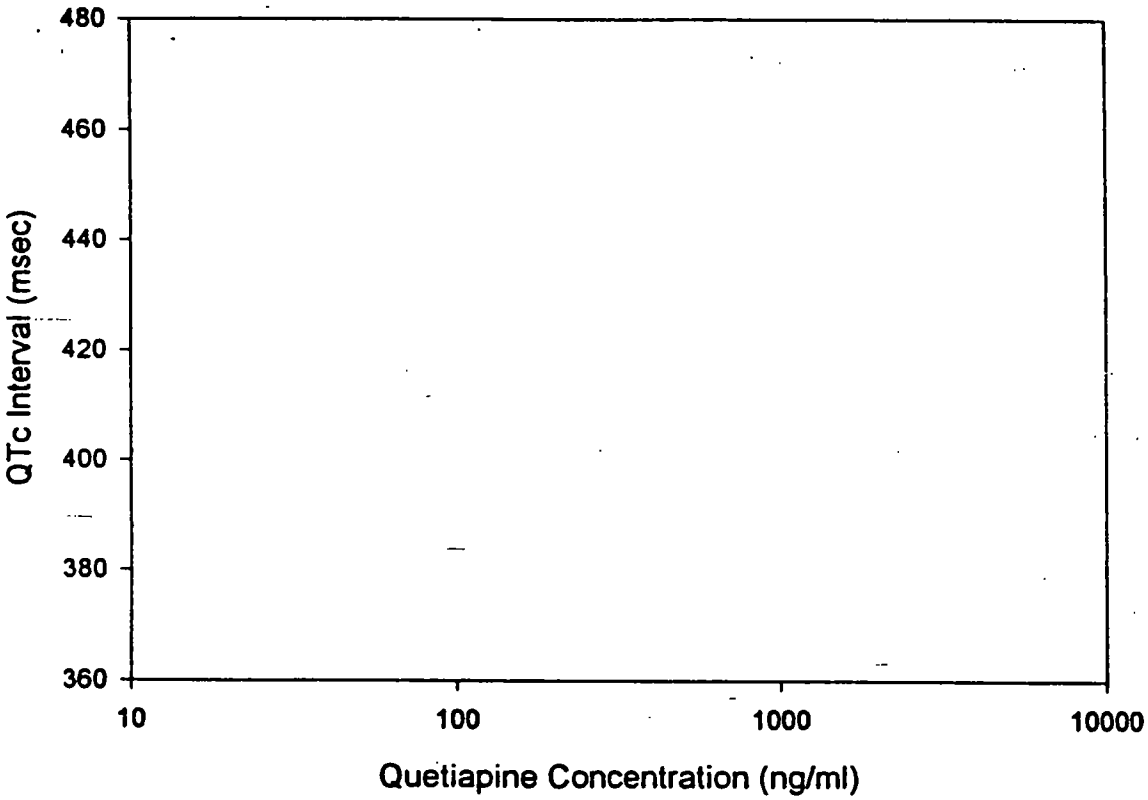
Intercept = 395.6947
Slope = 8.0848
r^2=0.02004478

Effect of Haloperidol on QT Interval



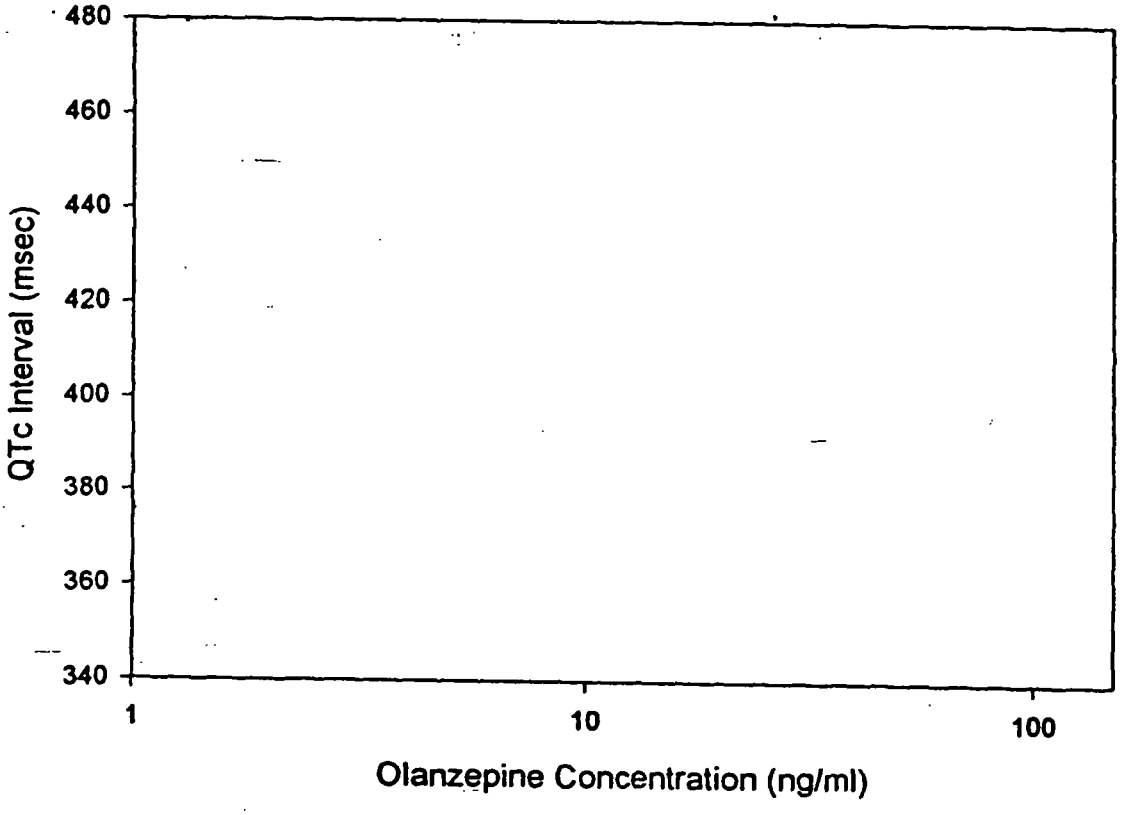
Intercept = 351.81535
Slope = 21.5923
r^2=0.1552740511

Effect of Quetiapine on QTc Interval



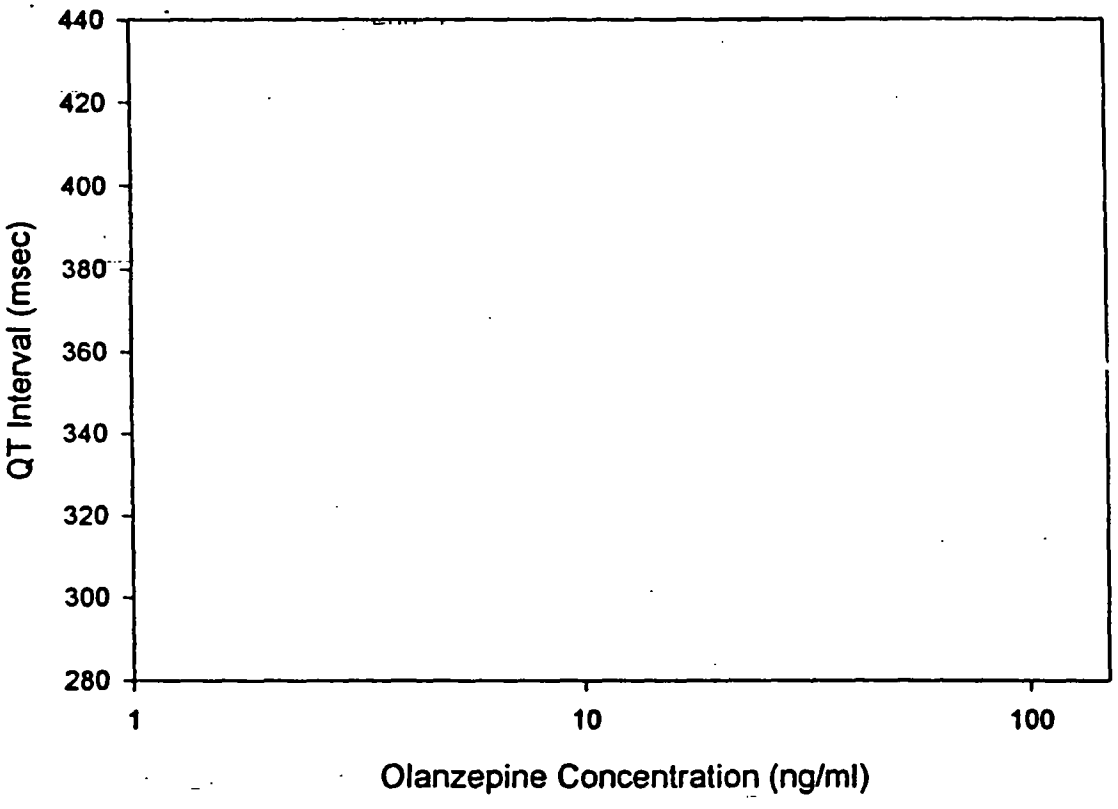
Intercept = 365.1656
Slope = 15.0783
r^2=0.1713726855

Effect of Olanzepine on QTc Interval



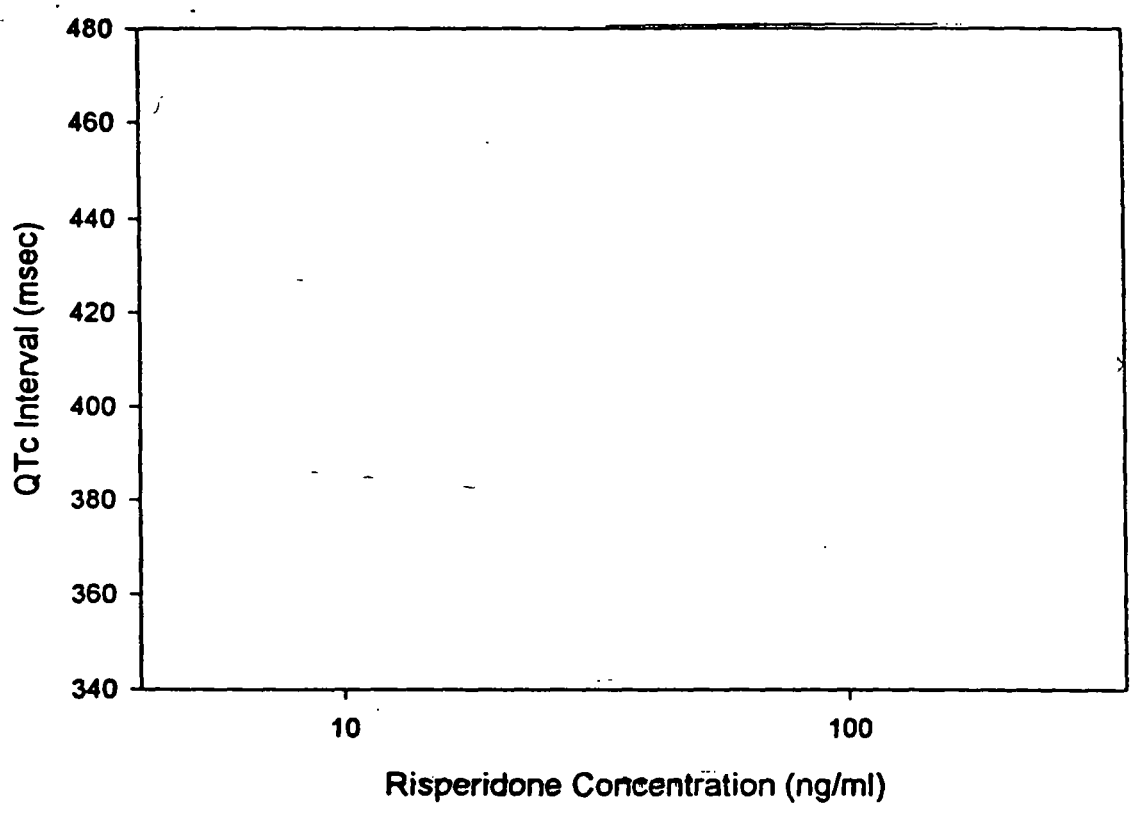
Intercept = 390.7492
Slope = 5.81969
r^2= 0.0177752817

Effect of Olanzepine on QT Interval



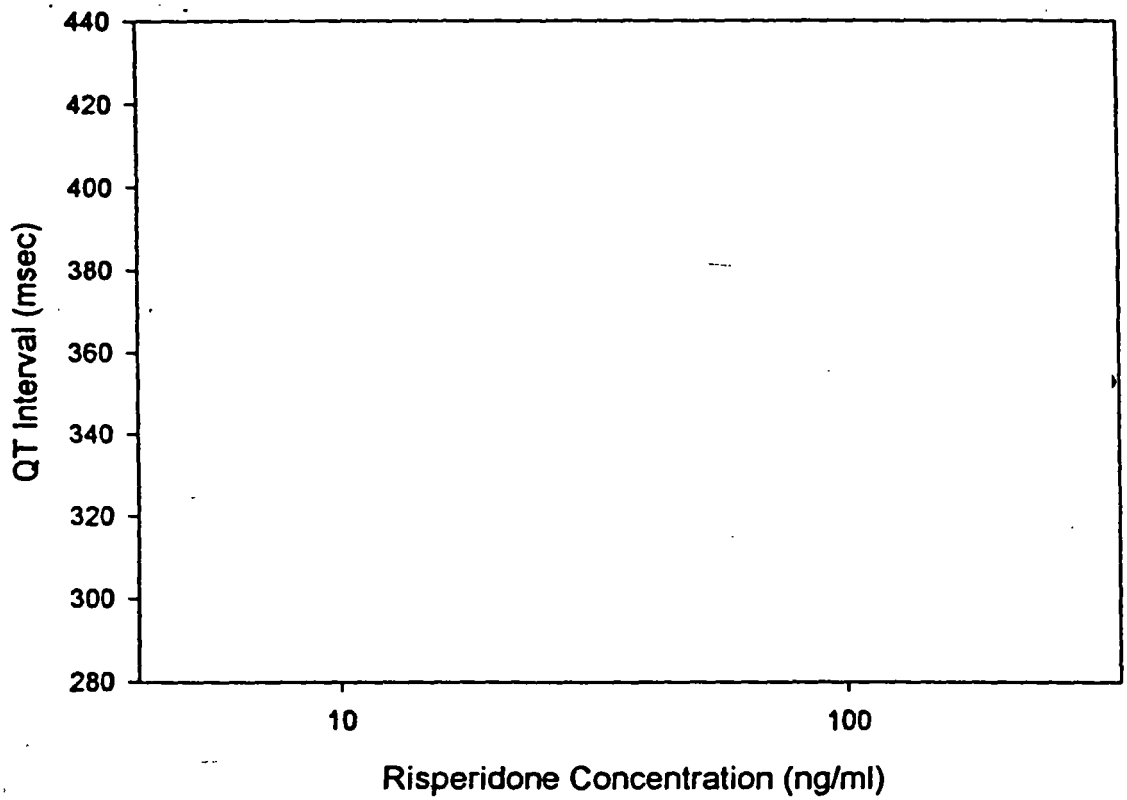
Intercept = 354.47023
Slope = 3.9619
r^2= 4.262398787e-3

Effect of Risperidone on QTc Interval



Intercept = 406.506151
Slope = -1.701107
r^2=1.2749627819e-3

Effect of Risperidone on QT Interval



Intercept = 367.81725
Slope = -3.157232
r^2=2.4245779374e-3

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 7, 1997
From: HFD-110
Subject: Comment on the Proposed ECG data displays for the ziprasidone NDA (#20-825)
Information Provided: volumes 2.1, 2.2
To: HFD-120

Background

HFD-110 has provided comments on the proposed submission of ECG QT and QTc interval data for NDA 20-825 (IND[ ]). The NDA has been submitted. HFD-120 requests comments on the submitted data displays.

Comments

- The sponsor has provided the data tables as proposed in the previous consult regarding the display of ECG data.
- Only post-randomization ECG recordings are provided in enclosure 3. The sponsor should provide baseline and any other post-randomization EKGs for the patients listed in enclosure 3.
- The data provided is sufficient to initiate a review of QT interval data. If a formal consult is requested to interpret QT interval data, additional pre-clinical and clinical information from the NDA will be needed from HFD-120.

/S/

Charles J. Ganley, M.D.

/S/

Raymond Lipicky, M.D.

cc: Division File
HFD-110/ganley
HFD-120/Hardemann/Laughren/