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APPLICATION NUMBER:

22-192

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-192
Submission Code	N
Letter Date	September 27, 2007
Stamp Date	September 27, 2007
PDUFA Goal Date	July 27, 2008
Reviewer(s) Name(s)	Michelle M. Chuen, M.D.
Review Completion Date	June 13, 2008
Established Name	Iloperidone
Trade Name	None
Therapeutic Class	Antipsychotic
Applicant	Vanda Pharmaceuticals Inc.
Priority Designation	S
Formulation	1, 2, 4, 6, 8, 10, and 12 mg Tablets
Dosing Regimen	12-24 mg/day administered BID
Indication	Schizophrenia
Intended Population	Adults with Schizophrenia

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

In accordance with 21 CFR 312.120, it is recommended that this application be granted Not Approvable status on the basis of insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling [314.125 (b)(4)]; and lack of substantial evidence consisting of adequate and well-controlled investigations that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling[314.125 (b)(5)].

1.1.1 Risk Management Activity

Since the undersigned reviewer is recommending a Not Approvable action, a risk management activity is not applicable.

1.1.2 Required Phase 4 Commitments

Since the undersigned reviewer is recommending a Not Approvable action, required phase 4 commitments are not applicable.

1.1.3 Other Phase 4 Requests

Since the undersigned reviewer is recommending a Not Approvable action, other phase 4 requests are not applicable.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

The efficacy of iloperidone in the treatment of adult patients with schizophrenia is based on Studies 3000, 3004, and 3005, which were randomized, double-blind, placebo- and active-controlled trials of about 6 weeks duration and Studies 3101 and B202, which were randomized, placebo-controlled trials of about 4 weeks duration. Studies 3000, 3101, and B202 were fixed-dose trials and Studies 3004 and 3005 were flexible-dose trials.

The evaluation of the safety of iloperidone in schizophrenia is based on four short-term trials: two fixed dose trials (3000 and 3101) and two flexible dose trials (3004 and 3005). Deaths, serious adverse events and dropouts due to adverse events were examined for the remaining 34

studies [Studies ILPB103, ILO5220105, ILO5220104, VP-VYV-683-1001, VP-VYV-683-1002, ILPB106, ILO5220110, ILPB101/101A, ILPB102, ILPB105, ILO5222301, ILPB203, ILO5220112, ILPB200, ILPB201, ILO522B210, ILO5220102, ILO5220103, ILO5220107, ILO5220108, ILO522A0109, ILP2001ST, ILP2001LT, ILP3007P1, ILP3007P2, ILP3001, ILP3002, ILP3003, ILO5222328, ILPB104, ILPB199, ILPB205, ILPB303, and ILPB202[1]] and the extension phases of Studies 3000, 3004, and 3005 (ILP3000LT, ILP3004 LT, and ILP3005 OLE).

1.2.2 Efficacy

There are 3 negative studies, 2 positive studies, and 3 studies in which an active comparator was found to be superior to iloperidone. Only one study showed an effect size of iloperidone comparable to the active comparator, with an OC analysis corroborating the MMRM analysis at most time points for the active comparator, but not iloperidone. Thus, the sponsor has not provided substantial evidence that supports the claim of short-term efficacy for the use of iloperidone in schizophrenia.

Of note, data from at least one of the Study 3101 sites was not considered to be reliable in support of this NDA, and 47% of the ITT patients in Study 3005 were contributed by sites where information on investigator financial interests were unobtainable.

1.2.3 Safety

Overall clinical experience is not adequate, with less than 64 patients and less than 22 patients having a duration of exposure for over 6 months and over 12 months, respectively, at the possibly effective dosage level of 24 mg/d. Thus, there is insufficient information to determine whether iloperidone is safe for use at this dose level.

Moreover, the integrity of the sponsor's existing safety data is questionable, given that an audit of patient CRFs, Narrative Summaries, and adverse event data listings revealed deficiencies in 7 out of the 8 examined, in addition to multiple deficiencies and discrepancies in the safety database which were incidentally noted.

Safety findings in the deaths, serious adverse events, and adverse events leading to dropout database include sudden deaths, seizures, arrhythmias, hypotension, syncope, priapism, and elevated creatine phosphokinase (CPK).

Safety findings in the controlled database include QTc prolongation, orthostatic hypotension, weight gain, anemia, high prolactin, and tachycardia.

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[1] Note that, although Study ILPB202 (also referred to as B202) was a placebo-controlled trial, the sponsor did not include it in their primary safety database.

1.2.4 Dosing Regimen and Administration

Study 3005 was a flexible dose study that examined nonoverlapping dose ranges of iloperidone (12 or 16 mg/d and 20 or 24 mg/d) versus placebo, administered on a twice-daily basis. Both dose groups produced a significant difference over placebo. For all dose groups, dosing for iloperidone began at 2 mg/d, and then increased to 4 mg/d, 8 mg/d, and 12 mg/d on Days 2, 3, and 4, respectively. At Day 5 and 6, the 20-24 mg/d dose group was increased to 16 mg/d and 20 mg/d, respectively.

Study 3101 was a fixed dose study of iloperidone that examined a dose of 24 mg/d of iloperidone versus placebo, administered on a twice-daily basis. This dose produced a significant difference over placebo. Dosing for iloperidone began at 2 mg/d, then increased to 4 mg/d, 8 mg/d, 12 mg/d, 16 mg/d, 20 mg/d, and 24 mg/d on Days 2, 3, 4, 5, 6, and 7, respectively.

1.2.5 Drug-Drug Interactions

There were no serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

1.2.6 Special Populations

The sponsor's subset analyses to evaluate the effect of age, gender, and race on treatment response was not appropriate due to varying primary efficacy variables among the 4 pooled studies, and due to the inclusion of schizoaffective patients in the analyses. Please see Section 6.1.4 for further details.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Iloperidone is a new chemical entity proposed for the treatment of schizophrenia. Iloperidone belongs to the chemical class of piperidinyl-benzisoxazole derivatives and has high (nM) affinity for $5HT_{2A}/NE_{\alpha 1}/NE_{\alpha 2c}/D_2/D_3/5HT_{1A}$ receptors in humans and acts as an antagonist at selected dopaminergic, serotoninergic, and adrenergic receptors.

The sponsor is seeking approval for treatment of adults with schizophrenia with a dosing regimen of 12 to 24 mg/day administered b.i.d. based on the results of 5 completed short-term fixed- and flexible-dose clinical studies.

2.2 Currently Available Treatment for Indications

The 17 moieties approved and available in the U.S. for the treatment of schizophrenia[2] are: chlorpromazine, prochlorperazine, perphenazine, trifluoperazine, thioridazine, fluphenazine, haloperidol, thiothixine, molindone, loxapine, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone. The 6 moieties that were approved but may no longer be available in the U.S. are: promazine, acetophenazine, propiomazine, piperacetazine, chlorprothixine, and mesoridazine.

2.3 Availability of Proposed Active Ingredient in the United States

Iloperidone has not been approved for use in the United States.

2.4 Important Issues with Pharmacologically Related Products

Some major safety issues related to atypical antipsychotics are increased mortality in elderly patients with dementia-related psychosis, suicidality in children and adolescents, clinical worsening and suicidality, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia and diabetes mellitus.

2.5 Presubmission Regulatory Activity

On 2/27/01, the Executive Carcinogenicity Assessment Committee (CAC) agreed with the sponsor that direct carcinogenicity testing of the metabolite, P95, was not necessary as long as P95 was negative in a full battery of genotoxicity tests and that no unique toxicities (compared to the parent compound) or preneoplastic findings are observed in the 6-mo oral toxicity of P95.

On 5/11/01, the Full CAC determined that the carcinogenic potential of iloperidone was adequately tested (assuming that the completed 2-year oral carcinogenicity studies in rat and mouse were adequate). Additional testing was recommended: two-week mouse data for pK rather than single dose of P95; additional carcinogenicity testing could be considered as a phase 4 commitment.

At a Pre-NDA meeting with Novartis on 6/28/01, it was noted that Study 3004 was positive while Studies 3000 and 3005 were negative. The sponsor was informed that, to preclude a refusal to file action, another positive study would be required.

[2] Per 5/8/08 email from Project Manager, Kim Updegraff.

Another Pre-NDA meeting with Novartis was held on 11/1/01, during which the sponsor's planned additional Phase 3 studies were discussed. Issues included the following:

- We recommended that the sponsor explore doses higher than 24 mg.
- We indicated several weaknesses in their proposed design, including focusing on the Tmax of the parent compound, ignoring metabolites; and not assessing the effects of a CYP 2D6 inhibitor and a CYP 3A4 inhibitor independently.
- We agreed to the use of quetiapine and ziprasidone as active controls.
- We suggested the sponsor provide further data to support the hypothesis that metabolite P95 is devoid of effects on cardiac repolarization.
- We recommended using both higher and lower dose groups to assess the potential for QT prolongation over the entire expected dose range.
- We suggested that the sponsor investigate the effects of iloperidone on fasting blood glucose.
- We stated that the presence of two negative trials, two positive trials, and three trials in which active control appeared superior to iloperidone would not be a compelling data set for the approval of iloperidone.
- We stated that if a study was powered to detect a very small effect, this would have to be evaluated in the context of previous data.

At another End-of-Phase 2/Pre-NDA meeting on 11/7/02, Novartis agreed to develop an approach to collect data on the pharmacokinetics of iloperidone at higher doses (e.g., 30 or 32 mg) in order to determine whether the plasma levels are comparable to those observed when 24 mg is maximally inhibited.

At a 4/28/05 Guidance meeting with Vanda, the sponsor was advised that a claim for a specific genetic subgroup would have to be prospectively demonstrated in two studies. The need to include active control arms in their efficacy trials, because of earlier findings in two trials of superiority of active comparators to iloperidone was discussed. The Division policy of requiring positive longer-term efficacy data at the time of submission of an NDA (responder status for at least 6 months before randomization, using a randomized withdrawal design) was also discussed. The sponsor was planning to develop [redacted] b(4)

At a statistical meeting held 7/26/05, the Division agreed that missing data imputed by the LOCF approach may introduce biases. The Division stated that we do not consider analysis based on a 2-part model appropriate, and that analysis via an MMRM may be acceptable, depending on whether or not data suggest violation of the MAR assumption. Also, the Division stated that, in addition to pre-specifying the primary analysis, the sponsor would need to pre-specify a number of sensitivity analyses to assess the impact of the missing data.

At the 9/7/05 End-of-Phase II meeting, for Study 3101, the Division recommended the following:

- that the sponsor include several fixed doses of iloperidone for Study 3101, because it was not clear that dose response for efficacy had been clarified
- that the statistical analysis plan would need to identify clearly the primary outcome or outcomes, and details and sequences of testing, as well as what would be needed to declare the study positive
- that showing specificity (i.e., a negative finding in the genetic subgroup with the marker) would be insufficient to support a claim of specificity in the subgroup of interest
- that they would need to have worked out all the details of a test kit that could be approved and marketed simultaneously with the approval and marketing of iloperidone
- that they would need full specification of the MMRM model, as well as justification for its use in this setting, along with sensitivity analyses and verification of the MAR assumption
- confirmation that their ITT sample would also require baseline assessment
- that they needed to submit a final SAP well before completion of the trial

The sponsor clarified that an interaction term in the model would be used in exploratory analyses, and not for the primary model

In addition, we did not provide a definitive answer on whether or not longer-term efficacy data would be needed, and indicated that we would very likely take iloperidone to a PDAC, given the safety concerns with this drug. We also agreed with a waiver for iloperidone for patients below the age of 13, and a deferral for the assessment of the effects of iloperidone in patients between 13 and 18 until assessments in adults have been completed.

At a 7/11/06 Executive CAC meeting, the Executive CAC concluded that:

- The full potential for carcinogenicity of the P95 metabolite has not been adequately tested, and that a follow-up study in rats is appropriate
- The sponsor should conduct a carcinogenicity study of the P95 metabolite with regard to P95 capacity for induction of hyperplasia and cellular proliferation in rats
- The 2-year carcinogenicity assessment was not accepted because its acceptance was contingent on the 6-month P95 study not showing a potential for cellular proliferation, which was not the case (it did show such a potential). The findings of the 6-month P95 study suggest a mechanism that could be relevant to tumorigenic activity in humans.

At a 9/12/06 EOPII/Type B meeting, the issues discussed include the following regarding study 3101:

- The sponsor agreed to use the commonly used MMRM approach as their primary analysis
- We conveyed that response profiles of the dropout patients were needed
- We conveyed that if there was any suspicion that the missing mechanism was non-ignorable during the Agency's review, then MMRM may not be deemed appropriate
- The sponsor agreed to pre-specify a detailed non-parametric method in the SAP in case there was doubt about the normality assumption
- We stated that, in pooling small sites, the sponsor may need to set a lower limit of number of patients in each site to avoid having unstable efficacy results

- The sponsor clarified that the pre-specified subgroup for CNTF is the genotype FS63 Ter(-)/Ter(-). Thus, the step-down primary analysis was the comparison between Ilo treated patients vs. placebo in those patients whose genotype is FS63 Ter(-)/Ter(-).
- The division noted that the study randomization did not account for stratification by patients' CNTF status, and that this comparison is only a descriptive summary and is not a randomized comparison. Dr. Laughren stated that the results of such a comparison could not be the basis for a claim in labeling.
- We asked the sponsor to provide data for justification regarding the diagnostic assay performance on sensitivity, specificity, and accuracy.
- We expressed concern for DNA samples being collected through the optional PG protocol, thus presenting many confounding factors, including potential differing characteristics between consented vs. non-consented patients. For example, early withdrawal patients might have consented initially at study randomization with different characteristics as compared to non-consented withdrawals. Unknown confounders that are implicit can introduce unknown bias that cannot be assessed. Such a patient selection process cannot yield a randomized comparison for confirmatory purpose.

In a 11/17/06 Type B meeting/EOPII to discuss the SAP for Study 3101,

- The Division agreed with the baseline-as-a-covariate MMRM model proposed in the SAP.
- The Division agreed with the methodology proposed for pooling sites.
- We accepted the sponsor's proposal for a randomization test based on the MMRM model with at least 1000 simulations to derive the p-value.
- We stated that the SAP for the primary objective appeared acceptable.
- The sponsor was told that if there goal was to include information based on the step-down primary objective into labeling, they would need to ensure the DNA sample quality for proper determination of genotyping results, and the sponsor agreed.
- The sponsor was asked to clearly state in the protocol that CNTF F63 Ter(-) genotype refers to FS63 Ter(-)/Ter(-).

In a 2/1/07 Pre-NDA Type B Meeting, the following were among the issues discussed:

- We noted that the purpose of subroup analyses for efficacy would be to explore the consistency of treatment effect across subgroups, and that they are not intended for claims in any subgroup. The non-inferiority analysis would also be considered exploratory.
- We indicated that the sponsor's plan to conduct MMRM analyses for sensitivity purposes would be acceptable.

In a 3/28/07 Advice Letter, the Division agreed that Vanda be allowed to file an NDA while the additional P95 carcinogenicity study was underway, under the conditions that the P95 two-year carcinogenicity study in rats be initiated before an NDA was filed, and until the P95 carcinogenicity assessment was completed, the product labeling must contain a strong statement describing the findings of hyperplasia seen in the 26-week rat study of the metabolite and indicate that this could progress to tumors with longer term treatment.

This NDA was submitted to the Agency on 9/27/07. The Filing Meeting was held on 11/9/07, and it was concluded that this supplement was fileable. The User Fee due date is 7/27/08.

A 4-Month Safety Update to the NDA was submitted on 1/23/08.

2.6 Other Relevant Background Information

Although the sponsor states that iloperidone has not been approved or marketed in any country, the undersigned reviewer was unable to locate any information specifically on withdrawal of the product in other countries, or on submission of marketing authorization applications to foreign regulatory agencies.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The sponsor claimed categorical exclusion from Environmental Assessment for this NDA. Per a 5/13/08 email from Donghao Lu, Ph.D., CMC reviewer, all CMC concerns have been resolved.

3.2 Animal Pharmacology/Toxicology

At the time of completion of this review, neither a Pharmacology/Toxicology review nor a draft of the review was available. Per a 5/15/08 email from Sonia Tabacova, Ph.D., Pharm/Tox reviewer, there were no unexpected findings.

3.3 Statistical Review and Evaluation

Phillip Dinh, Ph.D., is the Statistical Reviewer for this NDA. His final review is pending as of 5/13/08. Based on a draft of his review, he has indicated that efficacy for the schizophrenia subsample was demonstrated in Studies 3005 and 3101.

3.4 DSI Clinical Site Inspections

At the Filing Meeting on 11/9/07, Peiling Yang, Ph.D. Statistical Team Leader stated that she received a call from a [redacted] who had some concerns regarding the sponsor's data integrity. Dianne Tesch, DSI Consumer Safety Officer, contacted [redacted] Per Ms. Tesch's 5/13/08 email, [redacted] had nothing specific regarding any of the sponsor's study sites. [redacted], and [redacted] impression was that the sponsor would stop at nothing to get approval. However, [redacted] had no hard evidence or promising leads.

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The Division of Psychiatry Products selected 8 sites for inspection by the Division of Scientific Investigations (DSI). Five sites were from Study 3005 and 3 sites were from Study 3101. These sites are described in the table below, extracted from an 11/13/07 email from Dr. Phillip Dinh, Statistical Reviewer.

Investigator	Site	Study 3005 Site number (# of subjects)	Study 3101 Site number (# of subjects)
Tram Tran-Johnson, Pharm. D.	California Neuropsychopharmacology Clinical Research Institute San Diego, CA 92126 USA	545 (27 patients)	002 (31 patients)
Rick Mofsen, D.O.	Clinical Research, Inc. St. Louis, MO 63118 USA	612 (14 patients)	014 (25 patients)
Saibal Nandy, D.P.M., M.R.C.Psych.	631 Prospect Drive SW Medicine Hat, AB T1A 4C2 Canada	907 (8 patients)	NA
Miro Jakovljevic, M.D.	Clinical Hospital Centre Rebro Zagreb, 10000 Croatia	924 (9 patients)	NA
Vera Folnegovic-Smalc, M.D.	Psychiatric Hospital Vrapce Zagreb, 10000 Croatia	925 (25 patients)	NA
John Gilliam	International Clinical Research Associates, LLC 1601 Rolling Hills Dr Suite 201 Richmond, VA 23229-5011	NA	032 (11 patients)

Per a 3/20/08 email from DSI Division Director, Leslie Ball, M.D., following a meeting between DPP and DSI, the decision was made to cancel the inspection of Dr. Gilliam's site. He had been under investigation by FDA's Office of Criminal Investigation since an FDA inspection in 2003 (on a different NDA and different product) revealed possible falsification of study records. Dr. Gilliam reportedly signed a plea agreement admitting to falsification of study records, but before this could be posted with the court, he died on Feb. 2, 2008. The ORA field investigator for the NDA 22-192 related inspection of Dr. Gilliam wanted to know if the inspection of Dr. Gilliam's site still needed to be accomplished because OCI considered the site to be "volatile". Dr. Gilliam's research coordinator, ——— who reportedly recently ; ——— : as OCI b(6)

was negotiating a plea agreement with him on falsification of study records. ——— apparently signed a plea agreement and was scheduled to appear in court on 3/20/08.

DPP noted that our decision on approval did not depend on the data from Dr. Gilliam's site, so DSI agreed to cancel the inspection. DPP also stated that we would not need other sites to be inspected under this NDA. Because of the plea agreement(s) from this site on data falsification on a different study, DSI does not consider the data from Dr. Gilliam's site to be reliable in support of NDA 22-192.

Per a 4/28/08 email from Susan Thompson, M.D., DSI medical officer, DSI received the following information:

1. The inspection for Dr. Tram Tran-Johnson (sites 545 and 002) was complete; the EIR has not yet been received. There were numerous examples of lack of prompt reporting of AEs (not SAEs) and poorly completed AE forms were noted for both studies. On initial review, these were not felt to affect data integrity.
2. The inspection for Dr. Solnegovice-Smalc (site 925) was complete; the EIR has not yet been received. There were a number of protocol violations as well as deficiencies in preparing and maintaining adequate and accurate case records. The inspector's recommendation was VAI, and the preliminary review does not suggest that these violations will have an adverse effect on data integrity.
3. The sponsor inspection was complete; the EIR has not yet been received. The following was taken from the Form 483: "It was noted that Vanda personnel completed the clinical pharmacology report and a report amendment for this study, without possession of, or access to, the sourer data for the bioanalytical portions of the study. Instead, Vanda relied on uncompleted draft reports CIL0522 0108 and DMPK (US) R99 663, and supplemental information provided by Novartis. The Novartis draft reports and supplemental information contained errors including analytical accuracy and precision for iloperidone and two metabolites; Vanda transcribed the draft reports and supplemental information into their own clinical pharmacology report and Amendment #1, without being able to verify the contents."
4. Information on the inspections from the remaining 3 sites (612, 014, 907, and 924) was not available.
5. Dr. Thompson has not yet received the results of the for cause inspection of Dr. Jelana Kunovac's site 21.

The Clinical Inspection Summary (CIS) was not available at the time of completion of this review.

Of note, Clinical Pharmacology and Biopharmaceutics also requested that DSI inspections be performed due to the sponsor's providing conflicting study dates and the sponsor's supplying the same analytical data for study ILO522 108 fluoxetine and ILO522 107 ketoconazole. Following the DSI inspection, the sponsor submitted an Amended CSR for Study ILO522 108.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary safety database for iloperidone in the treatment of adult patients with schizophrenia is comprised of Studies 3000, 3004, 3005, and 3101. Deaths, serious adverse events and dropouts due to adverse events for the remaining 34 studies [Studies ILPB103, ILO5220105, ILO5220104, VP-VYV-683-1001, VP-VYV-683-1002, ILPB106, ILO5220110, ILPB101/101A, ILPB102, ILPB105, ILO5222301, ILPB203, ILO5220112, ILPB200, ILPB201, ILO522B210, ILO5220102, ILO5220103, ILO5220107, ILO5220108, ILO522A0109, ILP2001ST, ILP2001LT, ILP3007P1, ILP3007P2, ILP3001, ILP3002, ILP3003, ILO5222328, ILPB104, ILPB199, ILPB205, ILPB303, and ILPB202[3]] and the extension phases of Studies 3000, 3004, and 3005 (ILP3000LT, ILP3004 LT, and ILP3005 OLE).

The efficacy of iloperidone in the treatment of adult patients with schizophrenia is based on Studies 3000, 3004, and 3005, which were randomized, double-blind, placebo- and active-controlled trials of about 6 weeks duration and Studies 3101 and B202, which were randomized, placebo-controlled trials of about 4 weeks duration. Studies 3000, 3101, and B202 were fixed-dose trials and Studies 3004 and 3005 were flexible-dose trials.

4.2 Tables of Clinical Studies

A total of 38 clinical trials comprise this application (including the extension phases of Studies 3000, 3004, and 3005 (ILP3000LT, ILP3004 LT, and ILP3005 OLE). These trials are summarized in the table below.

TABLE 4.2.1: ILOPERIDONE STUDIES

Completed Phase I Studies	
Single-Dose	
ILPB103	Open-label crossover study to assess the effect of food on the pharmacokinetics of a 3 mg dose of iloperidone in 24 healthy adult subjects
ILPB199	Double-blind, placebo- and active-controlled three-way crossover study to document the time course of action of iloperidone, as reflected in changes in spontaneous EEG activity, in 5 adult patients with schizophrenia receiving a single oral 2 mg dose of iloperidone
ILPB104	German, single-center, double-blind, randomized, crossover study to investigate the effects of single doses of 1 and 2 mg iloperidone in comparison

[3] Note that, although Study ILPB202 (also referred to as B202) was a placebo-controlled trial, the sponsor did not include it in their primary safety database.

	to 75 mg chlorpromazine and placebo and to demonstrate a time-response curve of iloperidone on the central nervous system in 16 healthy adult subjects
ILO5220105	Open-label, randomized, 3-treatment, 3-period, 6-sequence crossover study to compare the pharmacokinetics of a 3 mg oral dose of iloperidone tablets under fed and fasted conditions and to determine the relative bioavailability of 3 mg of iloperidone oral tablets compared to 3 mg of iloperidone oral solution in 26 healthy adult subjects
ILO5220104	Open-label, randomized, two-cohort, three-period crossover study to characterize the pharmacokinetics of 3 mg of oral iloperidone in poor and extensive 2D6 metabolizers and to evaluate the interaction of 3 mg of oral iloperidone with a cytochrome P450 2D6-prototype substrate (80 mg of dextromethorphan) in 27 healthy adult subjects
VP-VYV-683-1001	Open-label, randomized, crossover study to evaluate the bioavailability of 3 mg of a new iloperidone controlled-release formulation relative to 3 mg of the immediate release formulation of iloperidone and to assess the effect of food on the controlled release formulation in 16 healthy adult subjects
VP-VYV-683-1002	Open-label, randomized, two-period, crossover study to evaluate the bioequivalence of 3 mg of naked iloperidone tablets relative to 3 mg of over-encapsulated iloperidone tablets in 24 healthy adult subjects
ILPB106	Open-label, randomized, crossover study to assess the bioequivalence of 3 mg doses of iloperidone capsules and tablets in 28 healthy [male] adult subjects
ILO5220110	Open-label, randomized, crossover study to evaluate bioequivalence between three low strength iloperidone formulations (1 mg) in 24 healthy adult subjects
ILPB101/101A	Double-blind, randomized, placebo-controlled, sequential study to assess the safety, tolerability, and pharmacokinetics of oral doses of 1, 3, and 5 mg of iloperidone in 27 healthy adult subjects
ILPB102	Open-label study to assess the safety and tolerability of 2 mg of iloperidone to 6 healthy adult subjects
ILPB105	Open-label study to investigate the absorption, distribution, metabolic profile, and excretion of 14C-iloperidone following oral administration of 3 mg of iloperidone labeled with 14C in 3 healthy adult subjects
ILO5222301	Open-label study to evaluate the absorption, distribution, metabolism and excretion of 14C-iloperidone following a 3 mg of iloperidone in 6 healthy adult subjects
ILO5220102	Open-label, parallel group study to compare the pharmacokinetics of iloperidone in 10 adult subjects with severe renal impairment with that in 13 matched healthy control subjects
ILO5220103	Open-label, parallel group study to compare the pharmacokinetics of iloperidone in 8 subjects with mild to moderate hepatic impairment with that in 8 matched healthy control subjects
ILO5220107	Open-label, randomized, crossover study to compare the pharmacokinetics of iloperidone and its metabolites following a 3 mg single dose of iloperidone alone and in combination with multiple-dose ketoconazole in 19 healthy adult

	subjects
ILO5220108	Open-label, crossover study to evaluate the single-dose pharmacokinetics of iloperidone and its metabolites for 3 mg of oral iloperidone administered alone and in combination with fluoxetine at steady state in 23 healthy adult subjects
Multiple-Dose	
ILPB203	Open-label, sequential-cohort, maximum tolerated dose, bridging study to assess the safety, tolerability, and steady-state pharmacokinetics of titration with iloperidone up to 32 mg/d over 29 days or up to 24 mg/d over 18 or 11 days in 24 adult patients with schizophrenia. Up to 8 male patients received the 32 mg/d dose for 3 days.
ILO5220112	Open-label study to assess the dose proportionality of iloperidone at steady-state following multiple doses of 2, 4, 8, and 12 mg b.i.d. of iloperidone over 41 days in 32 adult patients with schizophrenia
ILPB200	Double-blind, randomized, placebo-controlled study to evaluate the safety and tolerability of multiple 1-, 2-, and 4-mg bid oral doses of iloperidone over 28 days in 18 adult patients with schizophrenia
ILPB201	Double-blind, randomized, placebo controlled study to evaluate the safety and pharmacokinetics of multiple oral doses of up to 8 mg bid of iloperidone over 28 days in 38 adult patients with schizophrenia
ILO522B210	Double-blind, placebo-controlled, parallel group study to evaluate the safety and pharmacokinetics of single or multiple IM doses of two iloperidone depot variants at rising doses up to 750 mg in 98 adult patients with schizophrenia and schizoaffective disorder tolerating iloperidone tablets up to 24 mg qd. This was followed by 21 days of treatment with up to 24 mg qd of oral iloperidone.
ILO522A0109	Open-label, cross-over study to evaluate the pharmacokinetic or pharmacodynamic interaction of up to 8 mg bid of oral iloperidone and valproate administered separately and in combination over 25 days in 32 adult patients with schizophrenia
Completed Phase 2/3 Studies	
ILPB202	U.S., multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and tolerability at fixed doses of 2 mg bid and 4 mg bid in 104 adult patients (69 iloperidone, 35 placebo) with schizophrenia for up to 29 days
ILP2001ST	U.S., multicenter, double-blind, randomized, parallel-group study to evaluate the safety of two titration schedules over 28 days (to 12 mg/d) and then to compare the safety and efficacy of 6 mg bid and 12 mg qd regimens over 14 days and to explore the efficacy of iloperidone compared to haloperidol 7.5 mg bid in 120 adult patients (95 iloperidone, 25 haloperidol) with schizophrenia or schizoaffective disorder
ILP2001LT	Double-blind extension phase of Study ILP2001ST. 23 adult patients (17 iloperidone, 6 haloperidol) with schizophrenia or schizoaffective disorder were continued on iloperidone 6 mg bid or haloperidol 7.5 bid for up to 98 weeks
ILP3000ST	U.S., multicenter, double-blind, randomized, parallel-group, placebo- and

	active-controlled study to evaluate the safety and efficacy of three fixed doses of iloperidone (4, 8, and 12 mg/d) given bid for 42 days to 621 adult patients (370 iloperidone, 124 haloperidol, 127 placebo) with schizophrenia or schizoaffective disorder
ILP3000LT	Active-controlled extension phase of ILP3000ST. 232 adult patients (192 iloperidone, 40 haloperidol) with schizophrenia or schizoaffective disorder were continued on flexible doses of iloperidone 4-16 mg/d (if treated with iloperidone or placebo during ILP3000ST) or haloperidol 5-20 mg/d (if treated with haloperidol during ILP3000ST) given qd
ILP3004ST	International, multicenter, double-blind, randomized, parallel-group, placebo- and active-controlled study to determine the efficacy and safety of two nonoverlapping dose ranges of iloperidone (4-8 mg/d and 10-16 mg/d) and risperidone (4-8 mg/d) compared with placebo, administered bid over 42 days in 616 (307 iloperidone, 153 risperidone, 156 placebo) adult patients with schizophrenia or schizoaffective disorder
ILP3004LT	Active-controlled extension phase of ILP3004ST. 294 adult patients (219 iloperidone, 75 risperidone) with schizophrenia or schizoaffective disorder were continued on flexible doses of iloperidone 4-16 mg/d (if treated with iloperidone or placebo during ILP3004ST) or risperidone 2-8 mg/d (if treated with risperidone during ILP3004ST) given qd
ILP3005ST	International, multicenter, double-blind, randomized, placebo- and active-controlled study to determine the efficacy and safety of nonoverlapping dose ranges of iloperidone (12-16 mg/d and 20-24 mg/d) and risperidone (6-8 mg/d) compared with placebo, administered bid over 42 days in 706 adult patients (389 iloperidone, 157 risperidone, 160 placebo) with schizophrenia or schizoaffective disorder
ILP3007P1	U.S., single-center, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the safety and tolerability of 0.5 to 6 mg/d of iloperidone, given bid, compared to placebo over up to 31 days in 15 elderly patients (10 iloperidone, 5 placebo) with dementia
ILP3007P2	International, multicenter, double-blind, randomized, active-controlled study to evaluate the safety and tolerability of 0.5 to 6 mg/d of iloperidone, given bid, compared with 0.5 to 4 mg/d of risperidone, given bid over 4 weeks in 111 institutionalized elderly patients (68 iloperidone, 43 risperidone) with dementia
VP-VYY-683-3101	U.S. and India, multicenter, double-blind, randomized, placebo- and active-controlled study to evaluate the efficacy of a 24 mg/d iloperidone dose compared to placebo, administered bid over 28 days to 606 adult patients (303 iloperidone, 151 ziprasidone, 152 placebo) with schizophrenia. [ziprasidone-treated patients received 160 mg/d.] A step-down objective was to assess the efficacy of a 24 mg/d iloperidone dose in patients lacking the CNTF FS63Ter mutation versus patients who harbored the mutation.
ILP3001	International, multicenter, double-blind, randomized, parallel-group study to compare the antipsychotic effect of iloperidone 4-16 mg/d, given bid, with that

	of haloperidol 5-20 mg/d, given bid, over 52 weeks in 600 adult patients (454 iloperidone, 146 haloperidol) with schizophrenia or schizoaffective disorder
ILP3002	International, multicenter, double-blind, randomized, parallel-group study to compare the antipsychotic effect of iloperidone 4-16 mg/d, given bid, with that of haloperidol 5-20 mg/d, given bid, over 52 weeks in 557 adult patients (420 iloperidone, 137 haloperidol) with schizophrenia or schizoaffective disorder
ILP3003	International, multicenter, double-blind, randomized, parallel-group study to compare the antipsychotic effect of iloperidone 4-16 mg/d, given bid, with that of haloperidol 5-20 mg/d, given bid, over 52 weeks in 487 adult patients (365 iloperidone, 122 haloperidol) with schizophrenia or schizoaffective disorder
ILO5222328	U.S., multicenter, randomized, open-label, 5-arm, safety study to characterize the effect of iloperidone (at 8 mg bid and 12 mg bid) on the duration of the QTc interval over 3 weeks in 188 adult patients (106 iloperidone, 5 risperidone, 35 quetiapine, 34 ziprasidone) with schizophrenia or schizoaffective disorder
ILP3005 OLE	Active-controlled extension phase of ILP3005ST. 349 adult patients with schizophrenia or schizoaffective disorder were treated with up to 24 mg/d of iloperidone given qd for up to 110 weeks
ILPB205	Canadian, single-center, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the potential efficacy and safety of up to 16 mg/d of oral iloperidone over 42 days in 15 adult patients (12 iloperidone, 3 placebo) with schizophrenia or schizoaffective disorder
ILPB303	U.S., multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy of 4 mg bid and 8 mg qd of iloperidone administered to patients with schizophrenia or schizoaffective disorder for 42 days followed by open label treatment for one year

4.3 Review Strategy

A listing of the items examined during the course of this review is provided in Table 4.3.1. The 4-Month Safety Update was utilized only to determine extent of exposure. The remainder of the 4-Month Safety Update will be reviewed by Phillip Kronstein, M.D., Clinical Reviewer.

TABLE 4.3.1: ITEMS UTILIZED IN THE REVIEW	
Submission Date	**Items Reviewed**
September 27, 2007	Clinical Study Reports: Studies 3000, 3004, 3005, 3101, B202, ILPB103, ILO5220105, ILO5220104, VP-VYV-683-1001, VP-VYV-683-1002, ILPB106, ILO5220110, ILPB101/101A, ILPB102, ILPB105, ILO5222301, ILPB203, ILO5220112, ILPB200, ILPB201, ILO522B210, ILO5220102, ILO5220103, ILO5220107, ILO5220108, ILO522A0109, ILP2001ST, ILP2001LT, ILP3007P1, ILP3007P2, ILP3001, ILP3002, ILP3003, ILO5222328, ILPB104, ILPB199, ILPB205, and ILPB303 and the extension phases of Studies 3000, 3004, and 3005 (ILP3000LT, ILP3004 LT, and ILP3005 OLE) Financial Disclosure Certification Application Summary Case Report Tabulations (.xpt files) Case Report Forms
January 4, 2008	Email Responses to Filing Communication
January 23, 2008	4-Month Safety Update
April 7, 2008	Email Response to 3Apr08 Information Request Letter
May 14, 2008	Email Responses to Information Request

4.4 Data Quality and Integrity

The efficacy data from the two positive trials (after removing patients with a diagnosis of schizoaffective disorder) were examined by the statistical reviewer, Phillip Dinh, Ph.D. For Study 3101, none of the sites were found to negatively impact the efficacy outcome. Site 032 appeared to have the greatest impact; removing the site could push the results towards borderline (p=0.036). He was also able to identify several sites that could impact the outcome of Study 3005. The sites chosen by Dr. Dinh and the results of the DSI inspections are described in section 3.4.

Results of the adverse event safety data audit are described in section 7.2.7 of this review.

b(7)

4.5 Compliance with Good Clinical Practices

The undersigned reviewer was unable to locate information regarding ethical principles for Study B202.

Study 3000, 3004, and 3005 was performed in accordance with Novartis standard operating procedures, which were designed to ensure adherence to Good Clinical Practice, as described in the following documents:
1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US Code of Federal Regulations dealing with clinical studies (21 CFR including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983 and Hong Kong 1989).

Study 3101 was conducted in accordance with the Declaration of Helsinki (1964), amended 1975 (Tokyo), amended 1983 (Venice), amended 1989 (Hong Kong), amended 1996 (Somerset West); with the US Code of Federal Regulations governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and the obligations of clinical investigators (21 CFR 312); and with the International Conference on Harmonisation Guidance for Good Clinical Practice (Topic E6).

4.6 Financial Disclosures

For purposes of this NDA, Studies 3005 and 3101 are considered "covered clinical stud[ies]" in accordance with 21 CFR 54.2 (e).

Among the clinical investigators in these studies, three were identified by the sponsor as having financial arrangements that require disclosure[4]:

the principal investigator at Study Site , had equity interest in the form of pension plan IRA which exceeded $50,000 after 24 April 2000. It is unlikely that these arrangements biased the study results since this was a nd site contributed of the 671 ITT patients in the study. b(6)

, the principal investigator at Study Site), disclosed that institution received support from Novartis for other on-going studies for which served as principal investigator which had a monetary value greater than It is unlikely that these

[4] Of note, the number of ITT patients from each site was obtained from a 6/13/08 email from Dr. Phillip Dinh, Statistical Reviewer.

arrangements biased the study results since this was a [redacted] site contributed [redacted] of the 671 ITT patients in the study.

[redacted] the principal investigator at Study Site [redacted], disclosed that [redacted] received honoraria for speaking activities. It is unlikely that these arrangements biased the study results since this was a [redacted] trial and [redacted] site contributed [redacted] of the 671 ITT patients in the study.

Sixty seven (67) clinical investigators in these trials were identified by the sponsor as having unobtainable information on financial interests. The reasons for unobtainable information included:

- No response from investigational site(s) or principal investigator(s) despite the sponsor's attempts to contact them via letters, emails, and/or telephone calls
- Investigators no longer employed at the site and no forwarding address was available
- The financial disclosure form submitted was improperly completed by the investigators (i.e. investigators neglected to check either "yes" or "no" box indicating either presence or absence of financial interest)

These 67 investigators at 26 sites are identified in Appendix 10.4.1. The 26 sites contributed 313 (47%) of the 671 ITT patients in Study 3005 [5], and numbers of ITT patients contributed by each site are summarized below.

TABLE 4.6.1: STUDY 3005 SITES WITH UNOBTAINABLE INFORMATION ON INVESTIGATOR FINANCIAL INTERESTS

SITE	NUMBER OF ITT PATIENTS
502	9
509	15
511	33
544	7
545	49
559	21
564	5
629	0
851	0
852	9
853	15
858	3
860	8

[5] The number of ITT patients from each site was obtained from a 6/13/08 email from Dr. Phillip Dinh, Statistical Reviewer.

865	12
921	17
924	12
925	30
943	15
948	7
961	6
962	6
964	14
971	20
975	20
976	8
983	0

5 CLINICAL PHARMACOLOGY

Please note that a Clinical Pharmacology and Biopharmaceutics review was not available at the time of completion of this review, and the information below was obtained from the sponsor's Clinical Overview.

Per 5/14/08 emails from Andre Jackson, Ph.D., OCPB Reviewer, issues of concern included the genomic data analysis. The sponsor did not classify the extensive and poor metabolizers appropriately, and it was difficult to make meaningful comparisons between these two groups. In addition, the sponsor's proposed use of the CNTF gene to detect iloperidone efficacy was heavily influenced by placebo effect. Thus, use of this genotyping was questionable. Also, the hepatic study was confounded and needs to be repeated.

5.1 Pharmacokinetics

Absolute bioavailability of iloperidone has not been studied due to concerns about administering iloperidone intravenously, but based on data from an ADME study (ILO522 2301), it is estimated to be around 36% in the majority of the general population (i.e. individuals who are extensive CYP2D6 metabolizers). In poor CYP2D6 metabolizers, who constitute about 7% of the Caucasian population, absolute bioavailability is estimated at 54%. Exposure to iloperidone and its main metabolite P88 was significantly increased ($AUC_{0-\infty}$ by 57% and 95%, respectively), whereas exposure to its other main metabolite P95 was significantly decreased ($AUC_{0-\infty}$ by 80%) in poor CYP2D6 metabolizers as compared with extensive CYP2D6 metabolizers.

The pharmacokinetics of iloperidone was found to be dose-proportional in the range of 2 to 8 mg b.i.d. (4 to 16 mg daily), and that of P88 and P95 in the range of 2 to 12 mg b.i.d (ILO522 0112).

The deviation of iloperidone from dose-proportionality at 12 mg b.i.d. was small (1.5-fold increase in dose resulted in 1.74-fold increase in AUC_τ), so that for practical purposes, the pharmacokinetics of iloperidone can be considered dose-proportional over the entire range studied (2 to 12 mg b.i.d.).

Bioequivalence was generally demonstrated between the prototype, final marketed formulation (FMF) and overencapsulated formulations used in clinical trials. One study, ILO522 0110, demonstrated bioequivalence of the FMF tablet with its over-encapsulated version and with one prototype formulation used in earlier clinical studies. Another study, VP-VYV-683-1002, compared the pharmacokinetic characteristics of over-encapsulated tablets to naked tablets under fed conditions in healthy volunteers. BE criteria were met for all three analytes, except for C_{max} of iloperidone, which fell slightly outside the 80-125% limits (1.02-1.27), with the C_{max} values for the over-encapsulated tablets tending to be higher on average as compared to the naked tablets. For practical purposes, however, bioequivalence of naked and over-encapsulated tablets can be considered maintained in the fed state.

The food effect study (ILO522 0105), performed in healthy volunteers with a single 3-mg iloperidone dose of FMF tablet, showed that when iloperidone is administered with food, its absorption is slower (median t_{max} 3 h vs. 2 h in fasted state), but both the maximum plasma concentration (C_{max}) and area under curve (AUC) were essentially unchanged. Thus, from the point of view of pharmacokinetics, iloperidone can be given with or without food.

5.2 Pharmacodynamics

The first two HMR studies (ILPB101 and ILPB102) established that the maximum tolerated single dose in healthy volunteers was 3 mg, and that the dose-limiting events were dizziness occurring with or without orthostatic hypotension. Based on this experience, all later healthy volunteer studies were limited to the single 3-mg dose, and studies requiring higher doses were performed by titration in patients with schizophrenia.

Subsequent clinical pharmacology studies have determined that iloperidone is readily absorbed (t_{max} is 2-3 h after a single dose and about 1.5 h with multiple dosing), but undergoes a significant first-pass effect, so that absolute bioavailability is estimated to be approximately 36%. For purposes of clinical practice, the pharmacokinetics of iloperidone and its two main metabolites P88 and P95 can be considered dose-proportional in the dose range studied, i.e. from 2 to 12 mg b.i.d. (4 to 24 mg daily). The pharmacokinetic characteristics of iloperidone ($t_{1/2}$ approximately 18 h) and its active metabolite P88 ($t_{1/2}$ about 26 h) support once or twice-daily dosing. Two food effect studies (ILPB103 and ILO522 0105) indicated that with regard to pharmacokinetics, iloperidone can be taken with or without food.

A human ADME study (ILO522 2301) using [^{14}C]-iloperidone showed that there are multiple metabolic pathways for iloperidone. Of practical importance in humans are (1) the CYP2D6 pathway, which leads to formation of the most abundant metabolite in systemic circulation, P95, (2) a reduction pathway leading to the formation of the second most abundant metabolite, P88,

and (3) the CYP3A4 pathway, which produces metabolite P89 and probably other metabolites that are present in circulating blood in low quantities. This and other studies indicate that the total systemic exposure (AUC) to P95 is about 2.5 times that of iloperidone; however, this metabolite does not cross the blood-brain barrier, so it is believed to have no direct CNS activity. The total exposure to P88 is about 1.5 times that of iloperidone; it crosses the blood-brain barrier and has a similar receptor binding profile as iloperidone. Therefore, P88 is considered to be an active metabolite. The most abundant metabolites found in humans are the same as in the species used in toxicology studies. However, the main excretion route of products of iloperidone's metabolism is the kidney, different from rat and dog, in which most of the iloperidone dose is excreted with bile into feces.

The significant involvement of CYP2D6 in the metabolism of iloperidone is of practical importance to those individuals who have a genetic deficiency of this isoenzyme. These individuals are referred to as poor CYP2D6 metabolizers (PM), and constitute about 7% of the general population among Caucasians, and somewhat larger percentage in other races. The pharmacokinetic properties of iloperidone were compared between extensive and poor CYP2D6 metabolizers in a study specifically designed for that purpose (ILO522 0104) and the ADME study (ILO522 2301). Estimated absolute bioavailability of orally administered iloperidone was higher in poor than in extensive metabolizers (54 vs. 36%). Thus, poor CYP2D6 metabolizers (PM) have moderately higher exposure to iloperidone and P88, and much lower exposure to P95. In addition, in a separate interaction study (ILO522 0108) it was found that concomitant administration of a strong CYP2D6 inhibitor, fluoxetine, results in moderate increase in exposure to iloperidone and P88 ($AUC_{0-\infty}$ by 131% and 119%, respectively). In contrast, coadministration of another CYP2D6 substrate, dextromethorphan, had no effect on exposure to iloperidone or vice versa (ILO522 0104).

Other situations of modestly increased exposure to iloperidone and/or P88 are co-administration of strong inhibitors of CYP3A4 such as ketoconazole (ILO522 0107), hepatic impairment (ILO522 0103) and renal impairment (ILO522 0102). In renal impairment, the most noticeable change was an increase in exposure to P95, which is normally excreted into urine. All the above situations of increased exposure suggest caution in upward titration of patients with schizophrenia, but the need for dose adjustment should be considered in relation to overall clinical evaluation.

Iloperidone is about 95% bound to plasma proteins and the degree of binding was found to be unchanged in all situation tested, i.e. in subjects with renal and hepatic impairment, and during concomitant administration of iloperidone with ketoconazole.

A pharmacokinetic model was built (VP-VYV-683-3101-PK01) based on data from clinical pharmacology studies with intensive sampling and applied to data from a pivotal Phase 3 study for the purposes of population PK and concentration-response analysis. PK-PD modeling (VPVYV-683-3101-PK02) indicated a relationship between plasma concentrations of iloperidone and efficacy, as well as between concentrations and duration of QT interval.

Several bioequivalence studies demonstrated that formulations used in early clinical studies were bioequivalent to the final marketing formulation (FMF) used in later, pivotal studies.

Safety monitoring of clinical pharmacology studies revealed no tolerability or safety problems that would be unexpected from the point of view of experience from large clinical trials. The only possible exception, a case of sudden hearing loss (ILPB 104), was felt by the sponsor to not be related to iloperidone, based on both the absence of such cases in Phase 3 clinical trials and the results of animal studies investigating this issue.

5.3 Exposure-Response Relationships

See Section 8.1 for a discussion of efficacy dose response and Section 7.1.5.6 for a discussion of safety dose response.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This supplemental application seeks to establish the safety and efficacy of iloperidone in adult patients with schizophrenia.

6.1.1 Methods

The sponsor has conducted five multicenter studies to evaluate the short term efficacy of iloperidone in the treatment of adult patients with schizophrenia.

The sponsor also conducted three "supportive" studies (Studies 3001, 3002, and 3003), and performed statistical testing on a pool of the results from the three studies. The statistical plan was not pre-specified, and there was no placebo control. Thus, as discussed with Division Director Thomas Laughren, M.D. and Office Director Robert Temple, M.D. at the filing meeting on 11/9/07 and with Division Director Thomas Laughren, M.D. at the meeting to discuss efficacy on 1/25/08, these studies will not be considered supportive of the sponsor's efficacy claim and will not be described further.

6.1.2 General Discussion of Endpoints

Please see Section 2.5.

6.1.3 Study Design

Three pivotal studies (3000, 3004, and 3005) were randomized, double-blind, placebo- and active-controlled trials of about 6 weeks duration. Two pivotal studies (3101 and B202) were

randomized, placebo-controlled trials of about 4 weeks duration. Study 3000 used iloperidone doses of 2 mg BID, 4 mg BID, and 6 mg BID; Study 3004 used iloperidone doses of 2-4 mg BID and 5-8 mg BID; Study 3005 used iloperidone doses of 6-8 mg BID and 10-12 mg BID. Study 3101 used iloperidone doses of 12 mg BID; and Study B202 used iloperidone doses of 2 mg BID and 4 mg BID.

These 5 studies will be reviewed separately in Section 10.1. Of note, Studies 3000, 3004, and 3005 included schizoaffective patients. Efficacy analyses including only the schizophrenia patients were performed by Dr. Phillip Dinh, Statistical Reviewer.

6.1.4 Efficacy Findings

Predictors of Response
Since Study B202 was a negative study, it will not be discussed in this section. The sponsor performed subset analyses to evaluate the effect of the following variables on treatment response for the pool of Studies 3000, 3004, 3005, and 3101.

- Age (<50 vs. ≥50 years old)
- Gender
- Race (white, black, Asian, other)

However, due to varying primary efficacy variables among the four studies, pooling of all studies was not appropriate. Moreover, schizoaffective patients were included in the analyses.

Size of Treatment Effect
Treatment effect size was examined in terms of PANSS total score change from baseline to endpoint for Studies 3000, 3101, and B202. Treatment effect size was examined in terms of BPRS change from baseline for Studies 3004 and 3005. Results are summarized in Table 6.1.4.1 and 6.1.4.2 below. All results exclude schizoaffective patients.

TABLE 6.1.4.1: TREATMENT EFFECT SIZE AS EXPRESSED BY PANNS TOTAL SCORE, MEAN CHANGE FROM BASELINE AT ENDPOINT[6] (LOCF, ITT POPULATION)								
Study	Ilo 4 mg/d	Ilo 8 mg/d	Ilo 12 mg/d	Ilo 4-8 mg/d	Ilo 24 mg/d	Halo 15 mg/d	Zipr 160 mg/d	Pbo
3000[7,8]	9.2	4.8	10.1	NA	NA	12.9	NA	3.5
3101[9]	NA	NA	NA	NA	-12.01	NA	-12.27	-7.08
B202	-4.13	-18.2	NA	NA	NA	NA	NA	-6.68

Note: Ilo=Iloperidone; Halo=Haloperidol; Zipr=Ziprasidone; Pbo=Placebo

TABLE 6.1.4.2: TREATMENT EFFECT SIZE AS EXPRESSED BY BPRS TOTAL SCORE, LS MEAN CHANGE FROM BASELINE AT ENDPOINT (LOCF, ITT POPULATION)							
Study	Ilo 4-8 mg/d	Ilo 10-16 mg/d	Ilo 12-16 mg/d	Ilo 20-24 mg/d	Risp 4-8 mg/d	Risp 6-8 mg/d	Pbo
3004	5.77	6.51	NA	NA	10.31	NA	4.86
3005	NA	NA	7.4	8.8	11.4	NA	4.3

Note: Ilo=Iloperidone; Risp=Risperidone; Pbo=Placebo

The sponsor has provided evidence from two studies that suggests short-term efficacy of iloperidone in schizophrenia (Study 3005 and 3101). However, the effect size observed in Study 3005 was greater in active control than in both doses of iloperidone.

Studies 3000, 3004, and B202 failed to demonstrate the superiority of iloperidone over placebo in this condition. Moreover, in the two studies which included an active control arm, the active control was found to be superior to placebo.

[6] Day 42 for Studies 3000 and B202; Day 28 for Study 3101
[7] LOCF, ITT population
[8] LS Mean Change from Baseline
[9] MMRM, MITT population

The results of the five studies are summarized in Table 6.1.4.3 below.

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TABLE 6.1.4.3: SUMMARY OF EFFICACY RESULTS (STATISTICAL SIGNIFICANCE OF DRUG/PLACEBO DIFFERENCES AT FINAL ON-THERAPY ASSESSMENT																
Variable	**Dataset**	**Study**														
		3000 Ilo 4 mg/d	3000 Ilo 8 mg/d	3000 Ilo 12 mg/d	3000 Ilo 8 mg + 12 mg/d	3000 Halo 15 mg/d	3004 Ilo 4-8 mg/d	3004 Ilo 10-16 mg/d	3004 Risp 4-8 mg/d	3005 Ilo 12-16 mg/d	3005 Ilo 20-24 mg/d	3005 Risp 6-8 mg/d	3101 Ilo 24 mg/d	3101 Zip 160 mg/d	B202 Ilo 4 mg/d	B202 Ilo 8 mg/d
PANSS total score	MMRM	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**	*	NA	NA
	LOCF	tr	ns	*[10]	ns	**	NA	NA	NA	NA	NA	NA	NA	NA	ns	tr
	OC	NP	NP	NP	NP	NP	NA	NA	NA	NA	NA	NA	ns	tr	NP	NP
BPRS	LOCF	NA	NA	NA	NA	NA	ns	ns	**	*	**	**	NA	NA	NA	NA
	OC	NA	NA	NA	NA	NA	NP	NP	NP	**	*	**	NA	NA	NA	NA

Codes: ns= not significant ($p>0.10$)
tr= trend ($0.05<p\leq0.10$)
* = significant ($0.01<p\leq0.05$)
**= highly significant ($p\leq0.01$)
NA= not applicable
NP = not provided

[10] Please note that this was not the primary treatment comparison

Duration of Treatment
No study addressing the long-term efficacy of iloperidone in schizophrenia has been completed.

6.1.5 Clinical Microbiology

Since iloperidone is a solid oral formulation, this section is not applicable.

6.1.6 Efficacy Conclusions

There are 3 negative studies, 2 positive studies, and 3 studies in which an active comparator was found to be superior to iloperidone. Only one study showed an effect size of iloperidone comparable to the active comparator, with an OC analysis corroborating the MMRM analysis at most time points for the active comparator, but not iloperidone. Thus, the sponsor has not provided substantial evidence that supports the claim of short-term efficacy for the use of iloperidone in schizophrenia.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The evaluation of the safety of iloperidone in schizophrenia is based on four short-term trials: two fixed dose trials (3000 and 3101) and two flexible dose trials (3004 and 3005). Deaths, serious adverse events and dropouts due to adverse events were examined for the remaining 34 studies [Studies ILPB103, ILO5220105, ILO5220104, VP-VYV-683-1001, VP-VYV-683-1002, ILPB106, ILO5220110, ILPB101/101A, ILPB102, ILPB105, ILO5222301, ILPB203, ILO5220112, ILPB200, ILPB201, ILO522B210, ILO5220102, ILO5220103, ILO5220107, ILO5220108, ILO522A0109, ILP2001ST, ILP2001LT, ILP3007P1, ILP3007P2, ILP3001, ILP3002, ILP3003, ILO5222328, ILPB104, ILPB199, ILPB205, ILPB303, and ILPB202[11]] and the extension phases of Studies 3000, 3004, and 3005 (ILP3000LT, ILP3004 LT, and ILP3005 OLE).

Please see Table 4.2.1 for a summary of these investigations.

[11] Note that, although Study ILPB202 (also referred to as B202) was a placebo-controlled trial, the sponsor did not include it in their primary safety database.

7.1.1 Deaths

The sponsor tabulated deaths that occurred during treatment or within 30 days after the last dose of study drug. There were 23 deaths. Four (4) of these deaths occurred either prior to receiving study drug or prior to randomization. One (1) of these deaths occurred in a subject receiving placebo (cardiorespiratory failure due to pulmonary emboli), and three (3) of these deaths occurred in subjects receiving active-control (2 risperidone and one haloperidol). Thus, 15 deaths occurred in subjects receiving iloperidone. These patients are listed in the table below, extracted from the sponsor's submission.

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Patient ID	Age (yr)/ Sex/Race	Last Dose (mg/day)	Days of Treatment	Study Day of Death	Source [a]	Person Time [b]	Cause of Death/Comments
ILP3001-010-1012	39/M/W	8	215	215	1	Yes	SUICIDE On Study Day 210 the patient had no complaints of depression or suicidal thoughts. On Study Day 216 the patient committed suicide by jumping from his 10th floor flat window. The patient died instantly. The patient had no previous suicidal thoughts or attempts and had been mentally stable the day before the event. An autopsy was not performed. The investigator considered the event was not due to lack of efficacy or progression of the underlying illness and was not related to study medication.
ILP3001-094-1012	49/F/W	4	79	79	1	Yes	CARDIAC FAILURE On Study Day 91 the patient did not arrive for her study visit. The police were notified, entered the patient's house and discovered her dead body. An autopsy was performed which reported the cause of death as heart failure. The patient had no past history of heart failure, myocardial infarction or alcohol abuse. The investigator considered the death not related to study medication.
ILP3001-126-1001	59/F/W	16	126	Post-study Day 28	1	Yes	SUICIDE On Study Day 126 this patient was withdrawn from the study due to unsatisfactory therapeutic effect. Twenty-eight days later this patient committed suicide by drug overdose. An autopsy was performed confirming suicide by overdose with prothipendyl hydrochloride (a blood level of 9 µg/mL was detected).

Patient ID	Age (yr)/ Sex/Race	Last Dose (mg/day)	Days of Treatment	Study Day of Death	Source [a]	Person Time [b]	Cause of Death/Comments
ILP3002-017-1001	24/M/A	8	200	200	1	Yes	SUICIDE The patient was not reported to have any suicidal ideation or suicide attempts since his first admission to the study site. On Study Day 200, the patient was left home alone. Upon returning home, the patient's family found the patient hanging from a tree, deceased. There was no suicide notes left and, in the investigator's opinion, the patient's suicide was probably due to his delayed pension. No autopsy or toxicology report was generated.

Patient ID	Age (yr)/ Sex/Race	Last Dose (mg/day)	Days of Treatment	Study Day of Death	Source [a]	Person Time [b]	Cause of Death/Comments
ILP3002-056-1012	29/F/A	16	169	170	1	Yes	SUDDEN DEATH At study entry, the patient's ECG showed S-T segment elevation. Nevertheless, the patient was enrolled and began treatment with iloperidone in the fixed-titration phase. During her participation in the study, the patient presented with a buttock abscess and was treated with cloxacilline (Study Days 146 to 152); the abscess was completely recovered on Study Day 152. On Study Day 166, treatment was initiated for allergic rhinitis with an antihistamine, chlorpheniramine, 4 mg three times a day and an antihistamine/decongestant combination drug, Actifed (triprolidine 2.5mg ÷ pseudoephedrine 60mg), three times a day. Over the next three days, the patient's mother reported that the patient appeared weak, lethargic, and was sleeping in very late each day. On Study Day 170, the patient was found dead when her mother went to wake her in the morning; the cause of death was declared as psychosis. No autopsy was performed before the body was cremated, according to traditional local practice. Hence, the exact cause of this sudden death remains unknown.

Patient ID	Age (yr)/ Sex/Race	Last Dose (mg/day)	Days of Treatment	Study Day of Death	Source [a]	Person Time [b]	Cause of Death/Comments
ILP3002 092-1010	60/M/O	12	364	Post-study Day 3	1	Yes	SEPTICAEMIA On Study Day 309, the patient was re-admitted to hospital due to acute exacerbation of psychosis. Concomitant medication was given and the patient's condition was considered improved on Study Day 312. The patient continued to stay in the hospital as he remained floridly psychotic. The patient completed the trial on Study Day 363 and entered the extension phase of the study. On Post-study Day 2, the patient developed an acute condition of hypotension and subsequently went into coma. The patient died on Post-study Day 3. The cause of death was determined as septicaemia leading to shock and myocardial infarction. Prior to this event, the patient was not known to have a history of cardiovascular or respiratory diseases. No autopsy was performed on the patient and no relationship to study drug was suspected. During the course of the study, a single notable increase in urine protein was recorded at 30 mg/dL on Day 310 and this was not associated with any related adverse event. At the endpoint assessment, no further change in laboratory data was reported.

Patient ID	Age (yr)/ Sex/Race	Last Dose (mg/day)	Days of Treatment	Study Day of Death	Source [a]	Person Time [b]	Cause of Death/Comments
ILP3003-502-1037	31/M/W	12	454	455	1	Yes	DIABETES MELLITUS Approximately three months after starting the open label phase of the study, the patient presented with sweating, weakness and loss of appetite. Ten days later the patient was hospitalized with uncontrolled diabetes mellitus; cardiac arrest and death occurred on open label phase Study Day 92. The investigator did not suspect a relationship between diabetes mellitus and study medication.
ILP3003-533-1006	48/M/W	16	307 [c]	671	1	Yes	SUDDEN DEATH DUE TO CARDIO-RESPIRATORY FAILURE Approximately nine months after beginning the open label phase of the study, this patient experienced sudden death, attributed to cardio-respiratory failure. Autopsy results for this patient were not available. The investigator did not suspect a relationship between the sudden death due to cardio-respiratory failure and study medication.
ILP3003-537-1029	68/F/W	8	520	Post-study Day 5	1	Yes	PYLORUS OCCULSION Thirteen months after beginning the open label phase of the study, this patient presented with vomiting and dehydration resulting in hospitalization and eventual death five days later. The event was recorded as probable pyloric obstruction and death from pylorus occlusion. The investigator did not suspect a relationship between the death due to probable pyloric obstruction and study medication.

Patient ID	Age (yr)/ Sex/Race	Last Dose (mg/day)	Days of Treatment	Study Day of Death	Source [a]	Person Time [b]	Cause of Death/Comments
ILP3004-214-1010	33/M/B	8	787	Post-study Day 22	1	Yes	ACUTE RENAL FAILURE On open label phase Study Day 420 the patient was diagnosed with an HIV infection. On open label phase Study Day 423 the patient was hospitalized with acute renal failure and pulmonary tuberculosis at which time the patient was discontinued from the study. The patient's renal function deteriorated rapidly culminating in death 22 days after discontinuing from the study; cause of death was reported as acute renal failure. A relationship between the events and the study medication was not suspected.
ILP3005-508-1012	29/M/W	12	109 [d]	151	1	Yes	SUICIDE This patient died from a self-inflicted gunshot wound to the head three months after commencing the open-label phase of the study. He had previously experienced psychotic decompensation including paranoid bizarre delusions and auditory hallucinations. The patient had continuing depression that was positively treated. He was reported compliant with medication and psychotherapy. A relationship to study drug was not suspected.
ILP3005-612-1005	50/M/W	16	42	Post-study Day 4	1	Yes	STRUCK BY AUTOMOBILE Four days after the final dose of study medication, this patient was struck by an automobile while his own car was stalled on the side of the road; the patient died from injuries 29 days after completing the six-week study. A relationship to study drug was not suspected.

Patient ID	Age (yr)/ Sex/Race	Last Dose (mg/day)	Days of Treatment	Study Day of Death	Source [a]	Person Time [b]	Cause of Death/Comments
ILP3005-976-1002	55/M/W	12	158 [e]	200	1	Yes	SUDDEN CARDIAC ARREST On open label phase Study Day 140, this patient experienced a relapse of psychotic symptoms and required hospitalization. The patient was also suffering from several localized and systemic infections for which he received antibiotic treatment. The patient's psychotic condition deteriorated and he did not respond to study medication dose increases. He was permanently discontinued from the study on Study Day 158. Three days later, the patient experienced a sudden cardiac arrest with respiratory failure. Although successfully resuscitated, he did not regain consciousness and died of pulmonary edema three weeks later. A relationship to study drug was not suspected.
ILP3007-518-1001	83/M/W	4	33	34	1	No	VOLVULUS This patient had a past history of surgeries and abdominal adhesions. At Day 34 (ILO 4 mg/d), the patient was discontinued from the study and was hospitalized due to volvulus of the bowel. The patient died the next day due to volvulus.

Patient ID	Age (yr)/ Sex/Race	Last Dose (mg/day)	Days of Treatment	Study Day of Death	Source [a]	Person Time [b]	Cause of Death/Comments
ILP3007-752-1001	64/F/W	85	85	85	1	No	PNEUMONIA This patient had a past medical history of aspiration pneumonia. The patient discontinued the study on Day 85 because of pneumonia and consequently died the day after.

Listing includes all deaths occurring during drug exposure or within 30 days following discontinuation.
Cutoff Date = December 4, 2006; A = Asian; B = Black; F = Female, M = Male, NA = Not Applicable; O = Other; W = White
[a] 1 = primary source clinical trials; 2 = secondary sources
[b] Identifies patients (yes/no) for whom person-time data are available and are included in the mortality rate calculations.
[c] Patient ILP3003-533-1006 received Haloperidol 5-20 mg/day for 364 days prior to exposure to iloperidone during open label phase.
[d] Patient ILP3005-508-1012 received Risperidone 4-8 mg/day for 42 days of prior to exposure to iloperidone during open label phase.
[e] Patient ILP3005-976-1002 received Placebo for 42 days of prior to exposure to iloperidone during open label phase.
Source: Patient narratives

The Narrative Summaries for these subjects were reviewed. Ten deaths were considered possibly related to iloperidone treatment, and had three apparent general causes: suicide-related (4 deaths), cardiac-related (5 deaths), and diabetes mellitus-related (1 death). The deaths due to cardiac failure occurred in patients aged 29 to 60 (mean 48); at Study Days 170, 307, 91, Post-Study Day 3 (after 158 days of treatment), and Post-Study Day 3 (after 363 days of treatment); and at doses ranging from 4 to 16 mg/d. All of the cardiac-related deaths were sudden in nature.

The suicides occurred in patients at Study Day 216, Post-study day 28 (after 126 days of treatment), at Study Day 200, and at Study Day 109. More formal suicidality analysis may be considered, although the incidence of suicides observed in iloperidone-treated patients is well below the background rate of suicides in the schizophrenic population (estimated to be between 10% in 10 years to 5.6 - 10%. Given that there were 3210 patients treated, involving 2000 patient years, the rate of suicide in this study can be estimated to be about 0.2% a year.

The following are case summaries of the remaining 6 deaths considered possibly related to iloperidone treatment.

ILP3001-094-1012 (Cardiac Failure)
On Study Day 91 the patient did not arrive for her study visit. The police were notified, entered the patient's house and discovered her dead body. An autopsy was performed which reported complete cardiac dilatation and the cause of death as heart failure. The patient had no past history of heart failure, myocardial infarction or alcohol abuse.

Of note, review of the Narrative revealed that the patient was apparently taking iloperidone until around Study Day 91, but this is inconsistent with the numbers in the columns "Days of Treatment" and "Study Day of Death" in the table above.

ILP3002-056-1012 (Sudden Death)
At study entry, the patient's ECG showed S-T segment elevation. Nevertheless, the patient was enrolled and began treatment with iloperidone in the fixed-titration phase. During her participation in the study, the patient presented with a buttock abscess and was treated with cloxacilline (Study Days 146 to 152); the abscess was completely recovered on Study Day 152. On Study Day 166, treatment was initiated for allergic rhinitis with an antihistamine, chlorpheniramine, 4 mg three times a day and an antihistamine/decongestant combination drug, Actifed (triprolidine 2.5mg + pseudoephedrine 60mg), three times a day. Over the next three days, the patient's mother reported that the patient appeared weak, lethargic, and was sleeping in very late each day. On Study Day 170, the patient was found dead when her mother went to wake her in the morning; the cause of death was declared as "psychosis". No autopsy was performed.

ILP3002 092-1010 (Septicemia[12])

On Study Day 309, the patient was re-admitted to hospital due to acute exacerbation of psychosis. Concomitant medication was given and the patient's condition was considered improved on Study Day 312. The patient continued to stay in the hospital as he remained floridly psychotic. The patient completed the trial on Study Day 363 and entered the extension phase of the study. On Post-study Day 2, the patient developed an acute condition of hypotension and subsequently went into coma. He was found to have neutrophilia, significant drop in BP, and ST segment changes. Manual evacuation of impacted stool was performed and dexamethasone was administered. The patient died on Post-study Day 3. The cause of death was determined as septicaemia leading to shock and myocardial infarction. Prior to this event, the patient was not known to have a history of cardiovascular or respiratory diseases. No autopsy was performed on the patient and no relationship to study drug was suspected. During the course of the study, a single notable increase in urine protein was recorded at 30 mg/dL on Day 310 and this was not associated with any related adverse event. At the endpoint assessment, no further change in laboratory data was reported.

Review of this patient's CRF revealed the following:

1. On Study Days 7 and 14, the patient had a high CK (352 U/L and 273 U/L, respectively; reference range: 24-195 U/L)
2. The patient had a low WBC count from around Study Day 21 to Study Day 273 (3.0-3.7 x 10^9 cells/L; reference range 4.1-12.3 x 10^9 cells/L).
3. On Study Day 310, the patient had a normal WBC count (8.2 x 10^9 cells/L),with a neutrophil % of 82.6, and extremely high CK (8874 U/L). According to the lab results in the CRF, the MB fraction was pending, and blood culture, hospital records, and HIV test results were not included in the submission.
4. The patient received study drug up until and on Study Day 365 (the day he developed hypotension and coma), and did not discontinue study drug 2 days prior to developing hypotension and coma, as described in the Narrative.
5. On Study Day 365 (the day the patient developed acute hypotension and coma), WBC count was normal (5.9 x 10^9 cells/L), with a neutrophils % of 95.3. CK was 66 U/L.
6. No ECG's were included in the CRF.
7. Prior to the development of coma, the patient's blood pressures and heart rates were relatively stable at around 130/85 and 70, respectively.
8. The patient's blood pressure and pulse are recorded as 60/40 and 52, respectively, on Study Day 367.

Thus, there is no evidence for infection or septicemia for this case. It appears the main event was the acute development of profound hypotension.

[12] As detailed below, the undersigned reviewer thinks the likely cause of death was hypotension, not septicemia.

ILP3003-502-1037 (Diabetes Mellitus)
On Study Day 445, the patient presented with sweating, weakness, and loss of appetite and had experienced weight loss. On Study Day 455, the patient was admitted to the ICU where a nasogastric probe and orotracheal cannula were inserted. The patient required assisted ventilation. He was diagnosed with diabetes mellitus, and his blood glucose level was 500 mg% (reference range: 70-110 mg%). The patient received sodium chloride, ampicillin, sodium bicarbonate, and insulin treatment. On Study Day 457, the patient suffered from cardio-respiratory arrest following signs of tachydyspnea. Resuscitation and adrenaline, atropine and sodium bicarbonate treatments were unsuccessful.

Review of the CRF revealed the following:

1. This patient did not have a pre-existing diagnosis of diabetes mellitus.
2. At Study Day 273, the patient's ECG was found to be abnormal, with ST segment elevation and T wave inversion. The ECG was not included in the submission.
3. At Study Day 364, the patient's ECG was found to be abnormal, with T wave inversion. Also, CK was elevated at 398 IU/L (reference range: 24-195 IU/L). The ECG and CK-MB fraction was not included in the submission.
4. All CRF Serum glucose levels were normal, last reported on Study Day 364.
5. This patient's Adverse Events CRF reveals that he was hospitalized at Study Day 445, 10 days before the Narrative Summary reports he was hospitalized.

Thus, a primary cardiac cause of death is unlikely, but cannot be ruled out.

ILP3003-533-1006 (Sudden Death Due to Cardio-Respiratory Failure)
Approximately nine months after beginning the open label phase of the study, this patient experienced sudden death, attributed to cardiorespiratory failure. Autopsy results for this patient were not available.

ILP3005-976-1002 (Sudden Cardiac Arrest)
On open label phase Study Day 140, this patient experienced a relapse of psychotic symptoms and required hospitalization. The patient was also suffering from several localized and systemic infections for which he received antibiotic treatment. The patient's psychotic condition deteriorated and he did not respond to study medication dose increases. He was permanently discontinued from the study on Study Day 158. Three days later, the patient experienced a sudden cardiac arrest with respiratory failure. Although successfully resuscitated, he did not regain consciousness and died of pulmonary edema three weeks later.

7.1.2 Other Serious Adverse Events

Serious adverse events were defined per ICH guidances as those that were deemed life-threatening or resulted in death, resulted in hospitalization, resulted in a fetal anomaly or fetal loss, resulted in a condition that substantially interfered with the activities of daily living of a study subject, or were deemed an important medical event requiring medical or surgical intervention to prevent serious outcome.

Serious adverse events that occurred during treatment or within 3 days after the last dose of study drug were tabulated by reason.

Of a total of 4078 iloperidone-treated subjects and 672 placebo-treated subjects, 642 (16%) of iloperidone-treated subjects and 49 (7%) of placebo-treated subjects experienced approximately 235 adverse events classified as serious. A tabulation of the incidence of all sponsor-identified SAE's is provided in Appendix 10.5.1.

The Narrative Summaries for SAE's considered medically serious were reviewed. Of note, in the table of line listings of SAE's provided by the sponsor in the 5/14/08 email, the outcomes of deaths were noted as "Resolved". Twenty two SAE's were considered medically serious and possibly related to iloperidone treatment. They are listed in the table below, and can be grouped into 9 general categories: seizures (8 SAE's), arrhythmias (3 SAE's), hypotension (3 SAE's), syncope (2 SAE's), priapism (2 SAE's), increased CPK (1 SAE), MI (1 SAE), tachycardia (1 SAE), and dizziness (1 SAE). Case summaries follow the table. SAE's of suicidal ideation or suicide attempt are not summarized here, as uncontrolled data is difficult to interpret in the schizophrenic patient population.

TABLE 7.1.2.1:
SELECT ILOPERIDONE-TREATED PATIENTS WITH SERIOUS ADVERSE EVENTS

Patient	Age	Sex	Days to Onset	Dose at time of SAE (mg/day)	Serious Adverse Event (Verbatim term)
CILO522A2328-0522-00006	36	M	8	4-8	Supraventricular tachycardia
ILP2001-502-1005	42	F	6	10-16	Sinus arrhythmia (sick sinus syndrome)
ILP2001-507-1004	54	M	1079	4-8	Syncope episodes
ILP2001-507-1005	27	M	752	4-8	Priapism
ILP2001-511-1002	39	M	528	4-8	Grand mal seizure
ILP3000-526-1002	56	F	1098, 1217	10-16	Seizure, Altered state of consciousness (r/o seizure)[13]/ Respiratory failure
ILP3000-532-	40	M	5	4-8	Elevated CPK values

[13] Of note, this verbatim term was coded to a preferred term of depressed level of consciousness.

1006					
ILP3000-558-1004	59	F	46	10-16	Dizziness/nausea upon standing
ILP3001-011-1021	20	M	39	12	Orthostatic[14] hypotension (faintness)
ILP3001-026-1004	26	F	8, 9	4-8	Grand mal type epileptic seizure, Grand mal type epileptic seizure
ILP3001-054-1001	45	F	2	4-8	Syncope
ILP3001-097-1002	30	M	1 to 6	4-8	Tachycardia
ILP3001-098-1011	63	M	182	4-8	Orthostatic[15] collapse/hypotension
ILP3002-011-1014	33	F	3	4-8	Convulsive seizure
ILP3002-032-1004	25	F	5	4-8	Hypotensive episode
ILP3002-054-1015	21	M	135	10-16	Convulsion
ILP3002-063-1001	45	M	428	10-16	Myocardial infarct (no symptoms[16])
ILP3002-064-1032	25	F	292	10-16	Generalized tonic clonic convulsion
ILP3003-533-1008	47	M	7	4-8	Convulsion
ILP3003-626-1009	40	M	5	4-8	Arrhythmia heartbeat/abnormal high blood pressure
ILP3005-612-1022	44	M	555	4-8	Tonic-clonic seizure
ILP3005-853-1009	42	M	16	10-16	Priapism

CILO522A2328-0522-00006 (Supraventricular tachycardia)
The 36 year old male entered the study with a history of schizophrenia, anxiety, agitation, seasonal allergies, and headaches. The patient had no known past cardiac medical history. On Study Day 7, his 3-minute sitting radial pulse, recorded after the morning dose administration, was increased (128 bpm). On Study Day 8 following the morning dose of study medication, the

[14] Please note that review of the narrative revealed evidence of hypotension, but not orthostatic hypotension.
[15] Please note that review of the narrative revealed evidence of hypotension, but not orthostatic hypotension.
[16] Of note, according to the narrative, the patient had symptoms.

nursing staff reported the patient's pulse as too fast to count. A second pulse value of 200 bpm was obtained 15 minutes later. The patient denied any pain or discomfort but was mildly diaphoretic. An ECG revealed normal sinus rhythm and an abnormal QRS-T and T wave abnormality. His blood pressure was 133/42 mmHg and pulse rate 196 bpm. He was treated with adenosine 6 mg, inderal 40 mg, and iv normal saline and oxygen via nasal cannula. He also received lorazepam 2 mg for anxiety.

The patient was transferred to the emergency room, treated with cardizem and his pulse decreased to 97 bpm by 10 pm. A relationship to study medication was suspected and the patient was permanently discontinued from the study due to supraventricular tachycardia. Alternative antipsychotic treatment was initiated.

No ECG tracing was included in this patient's CRF.

ILP2001-502-1005 [Sinus arrhythmia (sick sinus syndrome)]
While hospitalized during the titration period of the study, the patient complained of palpitations and shortness of breath on Study Day 6. The patient reported a one-year history of palpitations. She was found to have orthostatic increases in her pulse rate of 20 to 30 bpm. There were 2 to 15 mm Hg differences in blood pressure with position change. Her ECG noted sinus arrhythmia and a cardiology consult was ordered and the patient was placed on Holter monitor. Her Holter monitor revealed "normal sinus rhythm, with rates between 53 and 136 bpm. Sinus arrhythmia was noted. There were moderately frequent isolated PVCs, occasionally with bigeminy." The investigator suspected a relationship between the event and iloperidone and she was prematurely discontinued from the study on Study Day 6.

Review of this patient's CRF revealed the following:

1. The screening ECG was obtained on —— and not on ——, as described in the narrative.
2. The screening ECG was read as "normal sinus rhythm", with a rate of 80 bpm, and not "normal sinus rhythm with sinus arrhythmia" as described in the narrative
3. The next ECG was obtained on —— and not on —— as described in the narrative.
4. The—— ECG was read as "normal sinus rhythm", with a rate of 59 bpm, and not "sinus arrhythmia" as described in the narrative.

b(6)

No ECG tracing was included in this patient's CRF.

ILP2001-507-1004 (Syncope episodes)
During the course of the long-term, double blind study, the patient reported
decreased or lost appetite, weight loss and depression. The patient was switched to the open-label extension phase of the study and began to receive 8.0 mg/d iloperidone. He developed syncopal episodes on open-label Study Day 279 and was hospitalized. All laboratory values were within normal ranges. He was treated and permanently discontinued from study medication. The patient recovered from the event and was discharged from the hospital the following day. The investigator viewed the syncopal episodes as severe and due to the study medication.

ILP2001-507-1005 (Priapism)
The patient developed priapism unrelated to sexual activity on study day 752, was hospitalized for treatment and the study medication discontinued on study day 756. CK values and a urine drug screen were not clinically significant. The patient had had four previous episodes of priapism over the preceding year which spontaneously resolved in 30 minutes with no treatment. The patient was considered recovered from the event by Post Study Day 30.

ILP2001-511-1002 (Grand mal seizure)
The patient developed an exacerbation of congenital ichthyosis with an infection on Study Days 389 and 398. He was hospitalized for each event and medically treated. On Study Day 437, the patient experienced an additional exacerbation of his chronic ichthyosis with cellulitis. He was hospitalized and received medical intervention. On Study Day 528, the patient passed out in his yard and was evaluated in an emergency room for a Grand Mal Seizure. He underwent EEG, blood analysis and x-ray evaluations that did not provide any clear evidence of the etiology of his seizure. A CT without contrast of the head was negative. The patient was treated with phenytoin.

ILP3000-526-1002 Seizure, Altered state of consciousness (r/o seizure)[17]/ Respiratory failure
On Study Day 185, the patient was hospitalized with worsening symptoms of schizophrenia. The patient recovered 11 days later and continued in the study. The patient was hospitalized again on Study Day 423 for worsening of schizophrenia accompanied by symptoms of increased anxiety, suicidal ideation and confusion. While she was hospitalized, she experienced a general convulsive seizure that lasted approximately 2 minutes. The patient sustained left periorbital ecchymosis and bruising to the forehead (bilaterally) and also experienced approximately one hour of postictal confusion. The event was considered life threatening and medically significant. A loading dose of phenytoin (300 mg followed by 400 mg) was initially administered, followed by a regimen of 100 mg given three times a day. The patient was discharged from the hospital on Study Day 433. On Study Day 547, the patient was noted to be suffering from an altered state of consciousness. It appeared that she had fallen out of bed bruising both knees. Laboratory tests revealed a decrease in oxygen saturation and an increase in the level of creatine phosphokinase. Sodium levels were also 119 (unit unspecified). The patient was transferred to the intensive care unit and intubated. Unspecified diagnostic tests were performed to determine the cause for the altered state of consciousness. A seizure was suspected. Eighteen hours later, the patient was extubated without sequelae. The event was considered life threatening and medically significant. Study medication was discontinued. The patient was released from the hospital two days later, outcome was not specified.

ILP3000-532-1006 (Elevated CPK values)
An adverse event of moderate anxiety, which was treated with lorazepam, was reported from Study Day 3 until Study Day 5. The patient's CPK value was elevated at screening (505 U/L)

[17] Of note, this verbatim term was coded to a preferred term of depressed level of consciousness.

with normal LDH, ALT and AST values. On Study Day 5, the patient was prematurely discontinued from the study secondary to unsatisfactory therapeutic effect. His CPK value at discontinuation was severely elevated (5,020 U/L) from baseline with an elevated LDH and normal ALT and AST values. There were no clinical manifestations of neuroleptic malignant syndrome (NMS). On Post Study Day 1, the patient received 8 mg of iloperidone in error. On Post Study Day 11, the patient's CPK reached its maximum value of 21,750 U/L, with an elevated ALT (peak of 289 U/L on Post Study Day 12). On Post Study Day 15, the patient was discharged. At discharge, his CPK value was 5,452 U/L. On post Study Day 23, the patients CPK was reported as 357 U/L. on Post-study Day 44, the patient's CPK value was 307. The patient's ECG remained normal; CK-MB fractions peaked at 6.5 ng/L (reference: ≤ 5 ng/mL) on Post Study Day 1; and total bilirubin levels remained within normal limits.

ILP3000-558-1004 (Dizziness/nausea upon standing)
On Study Day 44 the patient had severe postural dizziness and nausea and was hospitalized. She received non-drug therapy. On Study Day 55 the dizziness became less severe and she was discharged from the hospital. On Study Day 69 the dizziness resolved.

ILP3001-011-1021 [Orthostatic[18] hypotension (faintness)]
The patient's baseline blood pressure was 130/95, and remained relatively stable without any evidence of orthostatic hypotension. On Study Days 21 and 28, his blood pressure was 110/65 and 108/64, respectively, without any evidence of orthostatic hypotension. On Study Day 39, while under supervision at home, the patient fainted approximately 30 minutes after taking the evening dose of study medication, but did not lose consciousness. The patient did not sustain a head injury when he fainted. Blood pressure was recorded as 90/60 on that day, with a heart rate of 100 bpm. Orthostatic vital signs were not recorded. The patient recovered after an additional 30 minutes. The patient's hospitalization was prolonged. On Study Day 41 the patient returned to the psychiatric ward and recommenced iloperidone at a lower dose level (4 mg/d). On Study Day 75 the patient withdrew consent and discontinued from the study.

ILP3001-026-1004 (Grand mal type epileptic seizure, Grand mal type epileptic seizure)
On Study Day 8 the patient had an unwitnessed grand mal type epileptic seizure and was found lying on the floor. The patient lost consciousness for less than 1 minute. The patient was admitted to the ward where she was treated for nausea with pyridoxine. No other treatment was given. On Study Day 9, the patient had a second grand mal type seizure, which was witnessed by medical staff. The patient again complained of nausea. The results of a cranial CT and EEG were normal. Study medication was discontinued. On Study Day 10 she was discharged from the hospital on alprazolam, haloperidol, and carbamazepine for seizure prophylaxis.

ILP3001-054-1001 (Syncope)
Shortly after midnight on Study Day 2, the patient went to the nurses' station complaining of a headache. She collapsed onto the floor but did not lose consciousness and reported feeling weak.

[18] Please note that review of the narrative revealed evidence of hypotension, but not orthostatic hypotension.

The patient was helped to a chair where she sat for about a minute before losing consciousness. During the patient's loss of consciousness, no pulse could be felt, no breathing movements were seen and the patient did not respond to stimulus. After approximately 1 minute, the patient began breathing spontaneously, a strong pulse returned and she regained consciousness. Following the event the patient was fully oriented with no signs of confusion, a blood pressure of 130/86 mm Hg and pulse rate of 58 bpm. She vomited once. The patient was sent to the emergency room and was hospitalized overnight in a general ward for investigation. The event occurred 8 hours after the last dose of study medication and was witnessed by the investigator. Blood tests (including renal and liver functions) were within the normal range, with the exception of lymphocytes, monocytes, neutrophils, glucose, creatinine, potassium and chloride. Mild QT prolongation was found on the ECG immediately after the syncopic episode, but the ECG returned to normal after several hours. No other pathology was found and the patient returned to the psychiatric ward in a stable condition. Study medication was permanently discontinued immediately following the event on Study Day 2.

No ECG tracing was included in this patient's CRF.

ILP3001-097-1002 (Tachycardia)
On Study Day 1, the patient experienced the onset of increased pulse rate which worsened over the next 5 days. On Study Day 6 the patient had a sinus tachycardia of 152 bpm. The patient also developed a mild increase in body temperature with body tremor. On Study Day 7 the patient's condition showed minimal improvement and was withdrawn from study medication following recommendation by a cardiologist. On Post Study Day 7, the patient's heart rate had returned to within normal limits. The Investigator suspected that the event was related to the study medication.

ILP3001-098-1011 (Orthostatic[19] collapse/hypotension)
On Study Day 181 study medication was increased to 12 mg/d due to worsening of positive schizophrenic symptoms. On Study Day 182, the patient felt tired and fell. He was disoriented, with hypotension (BP of 100/70 mmHg) and a pulse of 46 bpm and was hospitalized. The patient remained disoriented and somnolent with an unstable BP in the range of 100-120/65-80 mm Hg. Neurological exam was normal. On Study Day 183 study medication was temporarily withdrawn, and the patient's conscious level mildly improved and BP stabilized at 120/70 mm Hg. Study medication was recommenced at a lower dose (8 mg/d) on Study Day 185 but an electrocardiogram revealed first degree heart block and the patient was permanently discontinued from the study on Study Day 185. Alternative anti-psychotic medication with quetiapine was started on Study Day 186. On Post Study Day 1, the patient collapsed and was found to be bradycardic with a pulse rate of 46 bpm. ECG showed sinus bradycardia and no heart block. The patient was admitted and quetiapine was discontinued. On Post Study Day 9 the patient was discharged from hospital. On Post Study Day 15 the sinus bradycardia had resolved and the patient had completely recovered from the event. The patient did not experience any further

[19] Please note that review of the narrative revealed evidence of hypotension, but not orthostatic hypotension.

episodes of hypotension, collapse, or sinus bradycardia. The investigator suspected the event was related to study medication.

No ECG tracing was included in this patient's CRF.

ILP3002-011-1014 (Convulsive seizure)
On Study Day 2, the patient was noted to be extremely weak and socially withdrawn and the study medication was temporarily interrupted. On Study Day 3, the patient had "seizure-like" manifestations prior to an EEG and experienced a seizure attack while the EEG procedure was performed. The EEG findings were consistent with a seizure disorder. The patient experienced an episode of generalised seizure in the morning of Study Day 4 and she was referred to the neurologist for co-management. The patient was permanently discontinued from the study due to this event and carbamazepine was commenced. On Post-study Day 1, the patient continued to experience occasional aura symptoms at reduced intensity. The patient was discharged from the hospital on Post-study Day 4 on standard medications for her psychiatric illness. On Post-study Day 66, the patient was reported to be well with no further seizure episodes.

ILP3002-032-1004 (Hypotensive episode)
On Study Day 2, the patient was noted to have tachycardia and palpitations. Her supine BP and HR were 124/82 and 110, respectively, and her 3 minute standing BP and HR were 88/44 and 76, respectively. From Study Days 2 to 4, the patient experienced several notably decreased blood pressures as well as increased pulse rates. On Study Day 5, she complained of giddiness and vital signs recorded one hour after the patient had taken the morning dose of study medication revealed a supine BP and HR of 127/88 and 110, respectively, and a 3 minute standing BP and HR of 55/35 and 106, respectively. Sitting HR at that time was 134 bpm, and 1 minute standing HR was 156 bpm. The patient was discontinued from the study due to the hypotensive episode as well as persistent tachycardia and palpitations. On Study Day 6, at the patient's end of study examination, her vital signs had normalised except for a notable recording of increased one-minute standing pulse rate. No significant ECG changes were observed in response to the notable change in vital signs. Following discontinuation from the study, the patient was prescribed amisulpride for psychosis and discharged from the hospital on Post-study Day 6. At follow-up on Post-study Day 19, the patient was reported to be psychiatrically stable with no further complaints of tachycardia, palpitations and giddiness.

ILP3002-054-1015 (Convulsion)
At study entry, the patient was not known to have a previous medical history and family history of seizures. On Study Day 133, the patient complained of headache, musculoskeletal chest pain and abdominal pain. On Study Day 135, the patient took two tablets of benzhexol and two capsules of study medication in the evening. At 23:00 hrs, he experienced a tonic seizure with loss of consciousness for a few seconds. The seizure, which was witnessed by the patient's mother, lasted for five minutes, during which the following manifestations were observed: eyes gazed upwards, salivation, straightened and rigid limbs, incontinence. The patient fell asleep after the seizure. Two hours later, the patient had another episode of seizure with similar manifestations. He was admitted to the hospital and placed under observation. The study

medication was temporarily withheld. Diagnostic tests were conducted and the results of electroencephalogram confirmed the occurrence of seizures. A CT scan of the brain was performed on Study Day 141 and the findings revealed a lacunar infarction at the right basal ganglia. According to the Investigator, the study drug may have reduced the seizure threshold in this patient with an intracerebral lesion. The patient was permanently discontinued from the study on Day 142 due to this event and did not experience another seizure attack after his discharge from the hospital.

ILP3002-063-1001 [Myocardial infarct (no symptoms[20])]
While hospitalized for a serious adverse event (accentuation of psychosis) experienced in the double blind phase the patient developed a serious episode of insomnia. During this time, the patient entered the open label phase of the study. Seven weeks after beginning the open label phase of the study, the patient presented with sudden onset of chest pain over the left precardium. An ECG revealed ST elevation and Q wave presence, indicating an inferior myocardial infarction.

ILP3002-064-1032 (Generalized tonic clonic convulsion)
At study entry, this patient was not known to have a medical nor family history of epilepsy. On Study Day 292, the patient was witnessed to have convulsions which lasted for five seconds. She was later diagnosed to have generalised tonic clonic seizure associated with salivation and post-ictal confusion. No further medical intervention was undertaken and the patient was permanently discontinued from the study due to this event on Study Day 293. Post-study laboratory and neurological assessments did not reveal any significant findings. No further seizure attacks were reported and the patient was considered recovered from this event. The Investigator suspected a relationship between the study medication and event because the patient's medical and family history was negative for epilepsy and she was not on any concomitant medication that could have precipitated the seizure attack. At follow-up on Post-study Day 143, the patient was noted to be psychiatrically stable with no reports of another seizure attack.

ILP3003-533-1008 (Convulsion)
During the placebo period the patient's clinical status did not show any changes. On Study Day 7, after displaying irritability and physical aggression, the patient developed signs of mental confusion and suffered a tonic-clonic convulsion (40 seconds duration) after which he remained confused and disoriented. He received intravenous diazepam. Following study medication discontinuation, the patient was transferred to a different ward where he was found to be dehydrated, and have suffered weight loss. EEG and brain CT scan reported no pathological findings. Approximately one month post-study, the patient experienced gastrointestinal bleeding and was diagnosed with hiatus hernia and erosive esophagitis. He developed severe symptoms of dysphagia and malnutrition. He experienced vomiting upon food ingestion and symptoms of epigastralgia. He died of food aspiration on Post Study Day 88.

[20] Of note, according to the narrative, the patient had symptoms.

ILP3003-626-1009 (Arrhythmia heartbeat/abnormal high blood pressure)
On Study Day 6, the patient suffered elevated systolic and diastolic blood pressures (180/120 mm Hg) and dizziness. The patient received treatment with sublingual nifedipine. Subsequent blood pressure values obtained were 160 / 110 mm Hg and "cardiac arrhythmia" was diagnosed. Later the same day the patient was re-evaluated and blood pressure values were normal at 130/80 and the "arrhythmia" had subsided. The study medication was discontinued on Study Day 6. On Post Study Day 1 blood pressure values were of 140 / 110 mm Hg and the patient was under observation. At the time of this report the event had not resolved. Followup information has been requested. The patient initiated treatment with captopril 50 mg day. Blood pressure values were 140 / 90 on Post Study Day 6. The patient's condition had improved as per the investigator. Arrhythmia was diagnosed upon physical examination on Post Study Day 1. The "arrhythmia" had no clinical manifestation and was not confirmed by an electrocardiogram. It was not considered a serious adverse event by the investigator. The patient was discharged on Post Study Day 8 under treatment with captopril 50 mg day. As per the investigator the patient had completely recovered from the event.

No ECG tracing was included in this patient's CRF.

ILP3005-612-1022 (Tonic-clonic seizure)
On Study Day 513, the patient experienced a tonic-clonic seizure and was subsequently hospitalized. The patient discontinued from the study due to the event and was treated with alternative antipsychotic medication. A month later, the patient was reported to have recovered with no further seizure activity.

ILP3005-853-1009 (Priapism)
On Study Day 16, the patient experienced the onset of priapism. This event was not reported until after Study Day 18 when he was hospitalized for symptoms of worsening schizophrenia. On Study Day 18, the patient was prematurely discontinued from the study due to unsatisfactory therapeutic effect. The hospitalization for treatment of his worsening schizophrenia was prolonged by the significant medical event of priapism. On Post-study Day 2, a urine drug screen was positive for cocaine. A consulting urologist reported a patient history of questionable Viagra use. Treatment for the adverse event of priapism included a urology consult, unsuccessful needle aspiration of the corpus cavernosa and subsequent surgical intervention (Winter procedure). The patient experienced a lowgrade fever and was treated with Keflex. On Post-study Day 6, the adverse event of priapism was considered completely recovered and the patient was discharged from the medical facility and on the same day readmitted to the psychiatric hospital for stabilization of worsening schizophrenia. On Poststudy Day 15, the adverse event of worsening schizophrenia was considered completely recovered and
the patient was discharged from the hospital.

SAE's for the open label extension portion of Study 3101 was provided in the 120-Day Safety update, which will be reviewed by Phillip Kronstein, M.D., Clinical Reviewer.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the pool of the double-blind phase of four of the placebo-controlled studies (Studies 3000, 3004, 3005, and 3101), overall dropout rates were highest in the iloperidone 4-8 mg/d group and lowest in the iloperidone 20-24 mg/d group [52% (308/587) of placebo patients, 64% (299/470) of iloperidone 4-8 mg/d patients, 45% (217/483) of iloperidone 10-16 mg/d patients, and 28% (111/391) of iloperidone 20-24 mg/d patients]. Dropout rates primarily due to lost to follow-up were roughly comparable [3% (18/587) of placebo patients, 4% (18/470) of iloperidone 4-8 mg/d patients, 3% (16/483) of iloperidone 10-16 mg/d patients, and 1% (5/391) of iloperidone 20-24 mg/d patients]. Dropout rates primarily due to adverse events were roughly comparable [6% (34/587) of placebo patients, 7% (31/470) of iloperidone 4-8 mg/d patients, 4% (20/483) of iloperidone 10-16 mg/d patients, and 5% (18/391) of iloperidone 20-24 mg/d patients]. Dropout rates primarily due to unsatisfactory therapeutic effect were lowest in the iloperidone 20-24 mg/d group [29% (173/587) of placebo patients, 30% (142/470) of iloperidone 4-8 mg/d patients, 22% (106/483) of iloperidone 10-16 mg/d patients, and 9% (37/391) of iloperidone 20-24 mg/d patients].

7.1.3.2 Adverse events associated with dropouts

Appendix 10.5.2 in Section 10.5 presents the incidence of dropouts due to adverse experiences in the pool of the double-blind phase of four of the placebo-controlled studies (Studies 3000, 3004, 3005, and 3101). Of note, the sponsor only included adverse events leading to dropout in 3 or more iloperidone-treated patients. Two adverse events that led to dropout occurred in at least 1% of iloperidone-treated patients and at a rate higher than that for placebo patients: dizziness (10-16 mg/d) and orthostatic hypotension (10-16 mg/d). No single adverse event led to dropout in greater than 2% of the iloperidone-treated groups.

A tabulation of treatment-emergent adverse events that led to dropout in the pool of all iloperidone studies was examined.[21] There were 29 adverse events (ventricular extrasystoles, angina pectoris, arrhythmia, atrioventricular block first degree, cardiac failure, cardiac failure congestive, cardio-respiratory arrest, myocardial infarction, supraventricular tachycardia, pyloric stenosis, small intestinal obstruction, volvulus, sudden death, pyrexia, chest discomfort, chest pain, blood creatine phosphokinase increased, hepatic enzyme increased, electrocardiogram QT prolonged, blood creatinine increased, liver function test abnormal, syncope, convulsion, grand mal convulsion, tonic clonic movements, suicidal ideation, suicide attempt, renal failure acute, and priapism) leading to dropout that were considered medically serious.

[21] Table 2 of the sponsor's Response to 4/3/08 Information Request Letter contained in their 4/18/08 submission

On 5/14/08, the sponsor responded to our 5/9/08 request for a line listing with associated narratives for the medically serious adverse events leading to dropout. There were 60 events in iloperidone-treated patients. These narratives were reviewed. Seven of these have been described previously under deaths and 34 of these have been described previously under SAEs. Out of the 19 remaining narratives, 10 adverse events leading to dropout were considered possibly related to iloperidone treatment, and can be grouped into 6 general categories: syncope (3 events), increased CK (2 events), increased liver enzymes (2 events), arrhythmia (1 event), cardiac-related (1 event), and priapism (1 event). These 10 adverse events leading to dropout are listed in the table below. Case summaries follow the table. Dropouts due to suicidal ideation or suicide attempt are not summarized here, as uncontrolled data is difficult to interpret in a schizophrenic patient population.

TABLE 7.1.2.2:
SELECT ILOPERIDONE-TREATED PATIENTS WITH ADVERSE EVENTS RESULTING IN DISCONTINUATION OF TREATMENT

Patient	Age	Sex	Days to Onset	Dose at time of SAE (mg/day)	Serious Adverse Event (Verbatim term)
ILP3005-937-1003	36	M	19	24	Ventricular extrasystole
ILP3002-041-1005	27	M	55	8	Cardiac related chest tightness
ILP3000-548-1010	31	M	14	8	Elevated CPK
ILP3002-003-1002	48	M	7	8	Three-fold increase in CK/ Hematuria
ILP3002-015-1003	31	M	7	8	Elevated liver enzymes
VP-VYV-683-3101 003-0033	25	M	14	24	Elevated liver enzymes
ILPB203-021-6102	27	M	1	2	Syncope
ILP3005-852-1006	29	F	12	20	Hypotension blood pressure[22]
VP-VYV-683-3101 017-0006	37	M	7	24	Syncope
VP-VYV-683-3101 007-0023	43	M	16	24	Priapism

[22] Please note that there was no evidence of hypotension in this patient's CRF. However, the patient did have a syncopal episode, and this verbatim term was coded to a preferred term of syncope.

ILP3005-937-1003 (Ventricular extrasystole)
The patient entered the study with no known medical history and was not receiving any concomitant medications. On study day 4 the patient suffered from a tachycardia while receiving 12 mg/d of study medication. On study day 8 the patient's study dose was increased to 24 mg/d. the patient's tachycardia resolved on study day 12. On study day 19 the patient suffered from ventricular extrasystoly and was sent to the cardiology unit via ambulance. The patient took the last dose of the study medication on study day 19. On study day 26 the patient had the termination visit.

ILP3002-041-1005 (Cardiac related chest tightness)
Prior to the study, the patient had no history of chest tightness or abnormal ECG, but did experience tachycardia. On study days 2, 4, 5, 7 and 28 the patient experienced notable raised pulse rates while standing less than a minute (range 120 to 141 bpm). On Study Day 5 the patient experienced palpitations and his sitting pulse rate increased notably. One dose of propranolol was administered. During a scheduled visit on Study Day 55, an abnormal ECG of depressed ST segment was noted for the patient and no treatment was introduced. On study Day 56, the patient started having tightness in his chest. ECG findings were borderline, and closer monitoring was recommended upon a medical consultation. On study Day 62, the patient's ECG recordings were again borderline. The investigator decided to discontinue the patient from the study on Day 64, due to the event and concern for the patient's safety. On post-study Day 3, the patient's study end-point ECG returned to normal and his chest tightness also subsided.

ILP3000-548-1010 (Elevated CPK)
The patient experienced one notable increased standing pulse rate on Study Day 17 (120 bpm) of the maintenance period when an adverse event of increased pulse was recorded. The investigator attributed the increased pulse rate to the patient's severe agitation, which began on Study Day 9 and was treated with lorazepam and chloral hydrate. The patient's agitation was ongoing at the time of termination from the study. The patient's normal screening CPK value (56 U/L) increased to 282 U/L on Study Day 14. His ECG was normal with a heart rate of 99 bpm. He had an increased standing pulse rate of 120 bpm. On Study Day 21, the patients CPK value increased to 608 U/L, and his ECG was read as normal with sinus tachycardia at a rate of 101 bpm. The investigator commented that the elevated CK was probably secondary to iloperidone. On Study Day 22, iloperidone was withheld after the morning dose. On study Day 23, the patient's CK value increased to 1446 U/L, with a normal CK-MB. The patient was prematurely discontinued from the study secondary to this event. No symptoms related to musculoskeletal or cardiac events were recorded at any time during the study. On Post Study Day 1, the patient's ECG was normal with a heart rate of 98 bpm. On Post Study Day 13, the patient's CPK value decreased to within normal range (137 U/L).

ILP3002-003-1002 (Three-fold increase in CK/ Hematuria)
The patient had no past medical history of renal or cardiac complications. On study Day 5, the patient was noted to have a low-grade fever that resolved without intervention. On study Day 7, the patient was noted to have haematuria on local urine dipstick result. Central laboratory results

from the same day revealed a three-fold increased CK (990 U/L). Urine RBC count was reported normal. KUB and ECG were performed. KUB result revealed no radio-opacities over the kidneys with possible radio-opacities in the bladder region. QT prolongation was evident from the ECG. On study Day 8, the Investigator discontinued the patient from the study due to the haematuria detected earlier and the persistent increased CK. On post-study Day 5, the patient's CK value returned to normal. On post-study Day 6, his midstream urine microbiology test was normal. The Investigator considered the patient's increased CK and haematuria related to the study medication. Additionally, the patient had been found to have low HB (0.38 v/v) and HCT (123 g/L) at screening. On study Days 7 and 8, his HB and HCT continued to notably decrease (0.32 v/v and 101 g/L, respectively). On post-study Day 5, as per local laboratory, the patient's HB continued to be low (10.7 g/dL). No results of HB or HCT were available thereafter.

ILP3002-015-1003 (Elevated liver enzymes)
At screening, the patient was noted to have icteric sclerae upon physical examination but vital signs and laboratory assessments were unremarkable. Notably increased ALT (560 IU/L) and AST (272 IU/L) levels and increased Alk Phos (191 U/L) levels were reported on Study Day 7. The Investigator decided to discontinue the patient from the study due to the notable increase in liver enzymes and the patient was asked to stop taking the study medication. The patient, however, continued to take the study medication until Study Day 14. Endpoint visit assessments were conducted on Study Day 15 (ALT 76 U/L, AST 18 U/L, and Alk Phos 129 U/L); the patient was prescribed Essentiale® for elevated liver enzymes and discharged from the hospital. No notable change in laboratory data and vital signs was recorded at time of discontinuation.

Review of the patient's CRF revealed normal total bilirubin results throughout the study.

VP-VYV-683-3101 003-0033 (Elevated liver enzymes)
The patient entered the study with a medical history of occasional acid reflux, backaches, headaches and numbness of the left arm, which were all ongoing during the study. On Study Day 14, the patient was noted to have elevated liver enzymes (ALAT = 166 U/L; ASAT = 63 U/L). On Study Day 19 an unscheduled laboratory assessment was conducted, and the patient's liver enzymes remained elevated (ALAT = 160 U/L; ASAT = 51 U/L). Labs were again repeated on Study Day 20, and ALAT levels remained elevated (140 U/L), but ASAT levels had decreased (40 U/L). The patient was discontinued from the study on Study Day 21 due to the elevated liver enzymes. The laboratory results from the end of study assessment showed elevated ALAT = 142 U/L and ASAT = 48 U/L. The event was considered resolved 4 days after study termination with ALAT = 88 U/L and ASAT = 32 U/L.

Bilirubin levels were not provided in the narrative or CRF.

ILPB203-021-6102 (Syncope)
The patient was a 27 year old white male. On 12 Sep 1995 (Study Day 1), the patient experienced mild dizziness and mild rhinitis. He also had a severe syncope, which lasted 2 to 4 seconds. These three events led to his permanent discontinuation from the study on that day. The

patient's dizziness and rhinitis resolved on the same day. The patient recovered from his syncope the following day.

ILP3005-852-1006 (Hypotension blood pressure[23])
On Study Day 12, the patient experienced a syncopal episode. The event was not treated and resolved the same day. Other adverse events reported during the study included drowsiness (Study Day 7 to Post Study Day 1), hypostatic blood pressure (Study Days 9 to 13) and dizziness (Study Day 7 to Post-Study Day 1). On Study Day 13, the patient was prematurely discontinued from the study due to the adverse events of drowsiness, syncopal episode, "hypostatic blood pressure", and dizziness. On Post Study Day 1, she was noted to have a notably low systolic blood pressure (88 mm Hg) after standing for less than one minute. No supine blood pressure was reported in the narrative.

Review of this patient's CRF revealed no evidence of orthostatic hypotension. The patient's BP remained relatively stable throughout the study at around 100/60, both supine and standing.

VP-VYV-683-3101 017-0006 (Syncope)
The patient entered the study with a long medical history that included a balance disorder and lightheadedness. On Study Day 7, the patient experienced an adverse event of orthostatic hypotension as noted by the investigator, as well as an episode of syncope that was considered moderate in severity. The patient's blood pressure was noted to be 103/71 mmHg in the supine position and 110/72 mmHg upon standing after 3 minutes. The patients pulse rate was 83 bpm in the supine position and 121 bpm upon standing after 3 minutes. The patient was discontinued from the study due to the syncope. The event was considered resolved 2 days later.

VP-VYV-683-3101 007-0023 (Priapism)
The patient entered the study with only an allergy to trazodone. Prior to baseline and continuing through the study, the patient experienced agitation and insomnia, both of which were secondary to schizophrenia, and was prescribed lorazepam and zolpidem tartrate. On Study Day 16, the patient complained of priapism, which was considered moderate in severity and was treated with cephalexin and hydrocodone plus acetaminophen. On the following day, the patient was discontinued from the study. The event was considered resolved on Post-study Day 1.

7.1.3.3 Other significant adverse events

The sponsor conducted a thorough QTc study, ILO5222328, which was reviewed by the Interdisciplinary Review Team for QT Studies. The sponsor also presented some QTc and ECG abnormalities data for the pool of Studies 2001, 2328, 3000, 3001, 3002, 3003, 3004, 3005, and 3101. However, this data is difficult to interpret, given that most of this data was not placebo-controlled. The QTc and ECG abnormalities data for the pool of the double-blind phase of

[23] Please note that there was no evidence of hypotension in this patient's CRF. However, the patient did have a syncopal episode, and this verbatim term was coded to a preferred term of syncope.

Studies 3000, 3004, 3005, and 3101 will be presented in Section 7.1.9.3. The sponsor also presented QTc data for Study 3101 by CYP2D6*4 genotype polymorphisms (see Table 7.1.3.3.1 below). However, given that this is a post-hoc analysis, its utility is questionable.

TABLE 7.1.3.3.1: SUMMARY OF QTCF INTERVAL DATA BY CYP2D6*4 GENOTYPE POLYMORPHISMS, STUDY 3101 (SAFETY POPULATION)

	Iloperidone		Ziprasidone		Placebo	
QTc Parameter	*GG* N=227	*non-GG*[a] N=69	*GG* N=111	*non-GG*[a] N=36	*GG* N=118	*non-GG*[a] N=27
Mean QTcF at BL (msec)	388.2	390.6	387.2	389.2	387.2	396.6
Mean QTcF change from BL at Day 14 (msec)[b]	+10.4	+15.0[c]	+11.7	+9.3	-0.2	-2.4
Mean QTcF change from BL at Day 28 (msec)[b]	+5.0	+12.9[d]	+6.0	+5.1	-2.2	-5.2
Mean QTcF change from BL at Endpoint (msec)[b]	+5.6	+11.9[e]	+5.7	+6.7	-1.4	-3.6
Mean maximum QTcF change from BL (msec) (min-max)	+14.2 (-72, 68)	+23.6[d] (-31, 53)	+11.5 (-79, 84)	+15.1 (-28, 40)	-1.3 (-73, 45)	-5.5 (-35, 32)
N (%) with change in QTcF from <500 msec at BL to >500 msec post-BL	0	0	0	0	0	0
N (%) with QTcF >500 msec at both BL and post-BL	0	0	0	0	0	0
N (%) with ≥15% increase in QTcF from BL	2 (0.7%)	0	1 (0.7%)	0	0	0

Data Source: Study Report VP-VYV-683-3101 Table 10.5.1-1e through Table 10.5.1-4e
BL=baseline
[a] Non-GG subgroup comprised of *CYP2D6*4 (1846G>A) GA* and *AA* genotypes combined
[b] Number of patients with postbaseline data varied at each time point
P-values based on ANCOVA comparing ILO *CYP2D6*4 (1846G>A) GG* vs *non-GG* genotype groups. Model includes phenotype and Baseline (as a covariate)
[c] p=0.008 [d] p=0.002 [e] 0.009

The sponsor conducted analyses of adverse events of cardiovascular adverse events, seizures, extrapyramidal symptoms, metabolic changes (elevated prolactin, hyperglycemia, and hypoglycemia), rash and Steven-Johnson's syndrome, and exacerbation of schizophrenia. The following tables summarize the sponsor's analyses that had some clinical utility. However, given that these analyses included data that was not placebo-controlled, for the most part, they are difficult to interpret.

TABLE 7.1.3.3.2: SAFETY PROFILE FOR PATIENTS WITH CARDIOVASCULAR ADVERSE EVENTS, STUDIES 2001, 2328, 3000, 3001, 3002, 3003, 3004, 3005, AND 3101 (SAFETY POPULATION)

Number (%) of patients with:	Placebo (N=587)	ILO Comb. (N=3210)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Cardiac AE	23 (3.9%)	294 (9.2%)	23 (4.2%)	11 (3.5%)	21 (11.4%)
Severe cardiac AE	2 (0.3%)	25 (0.8%)	3 (0.5%)	1 (0.3%)	1 (0.5%)
Drug-related cardiac AE	12 (2.0%)	190 (5.9%)	12 (2.2%)	5 (1.6%)	17 (9.2%)
Serious cardiac AE	6 (1.0%)	22 (0.7%)	1 (0.2%)	1 (0.3%)	0
Serious drug-related cardiac AE	3 (0.5%)	9 (0.3%)	0	1 (0.3%)	0
Dose reduction/interruption	3 (0.5%)	28 (0.9%)	3 (0.5%)	0	1 (0.5%)
Tx discontinued for cardiac AE	3 (0.5%)	35 (1.1%)	2 (0.4%)	2 (0.6%)	1 (0.5%)
Death due to cardiac AE	1 (0.2%)	3 (0.09%)[a]	0	0	0

Data Source: ISS Table 7.5.1, ISS Table 21.1.1, ISS Table 21.2.1, ISS Table 21.3.1, ISS Table 21.4.1, ISS Table 21.5.1, ISS Table 21.6.1, ISS Table 21.7.1, ISS Table 21.8.1 and ISS Listing 1.

Table includes data from all phases of Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101 and period 1 of 2328.

Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone

[a] Includes 2 cardiac-related sudden deaths (ILP3003 533-1006 and ILP3005 976-1002).

TABLE 7.1.3.3.3: SAFETY PROFILE FOR PATIENTS WITH SEIZURES, STUDIES 2001, 2328, 3000, 3001, 3002, 3003, 3004, 3005, AND 3101 (SAFETY POPULATION)

Number (%) of patients with:	Placebo (N=587)	ILO Comb. (N=3210)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Seizure AE	2 (0.3%)	13 (0.4%)	1 (0.2%)	1 (0.3%)	0
Severe seizure	1 (0.2%)	8 (0.2%)	1 (0.2%)	1 (0.3%)	0
Drug-related seizure	1 (0.2%)	1 (0.1%)	0	0	0
Serious seizure AE	2 (0.3%)	10 (0.3%)	1 (0.2%)	0	0
Dose reduction/interruption	0	0	0	0	0
Tx discontinued for seizure	2 (0.3%)	7 (0.2%)	1 (0.2%)	0	0
Death due to seizure	0	0	0	0	0

Data Source: ISS Table 21.1.1, ISS Table 21.2.1, ISS Table 21.3.1, ISS Table 21.4.1, ISS Table 21.5.1, ISS Table 21.6.1, ISS Table 21.7.1 and ISS Table 21.8.1

Table includes data from all phases of Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101 and period 1 of Study 2328 (treatment without metabolic inhibitors).

Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone

TABLE 7.1.3.3.4: SAFETY PROFILE FOR PATIENTS WITH EXTRAPYRAMIDAL SYMPTOMS, STUDIES 2001, 2328, 3000, 3001, 3002, 3003, 3004, 3005, AND 3101 (SAFETY POPULATION)

Number (%) of patients with:	Placebo (N=587)	ILO Comb. (N=3210)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
EPS AE	68 (11.6%)	600 (18.7%)	326 (59.7%)	93 (29.9%)	45 (24.5%)
Severe EPS AE	2 (0.3%)	33 (1.0%)	66 (12.1%)	7 (2.3%)	2 (1.1%)
Drug-related EPS AE	56 (9.5%)	476 (14.8%)	305 (55.9%)	80 (25.7%)	44 (23.9%)
Serious EPS AE	0	11 (0.3%)	11 (2.0%)	4 (1.3%)	0
Tx discontinued for EPS AE	2 (0.3%)	15 (0.5%)	29 (5.3%)	4 (1.3%)	3 (1.6%)
Death due to EPS AE	0	0	0	0	0

Data Source: ISS Table 21.1.1, ISS Table 21.2.1, ISS Table 21.3.1, ISS Table 21.4.1, ISS Table 21.5.1, ISS Table 21.6.1, ISS Table 21.7.1 and ISS Table 21.8.1

Table includes data from all phases of Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101 and period 1 of Study 2328 (treatment without metabolic inhibitors).

Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone

TABLE 7.1.3.3.5: SAFETY PROFILE FOR RASH ADVERSE EVENTS, STUDIES 2001, 2328, 3000, 3001, 3002, 3003, 3004, 3005, AND 3101 (SAFETY POPULATION)

Number (%) of patients with:	Placebo (N=587)	ILO Comb. (N=3210)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Rash AE	20 (3.4%)	88 (2.7%)	11 (2.0%)	13 (4.2%)	3 (1.6%)
Severe rash AE	0	4 (0.1%)	0	0	0
Drug-related rash AE	9 (1.5%)	19 (0.6%)	2 (0.4%)	4 (1.3%)	2 (1.1%)
Serious rash AE	0	0	0	0	0
Serious drug-related rash AE	0	0	0	0	0
Dose reduction/interruption for rash	0	2 (0.1%)	0	1 (0.3%)	0
Tx discontinued for rash AE	1 (0.2%)	4 (0.1%)	0	0	0

Data Source: ISS Table 21.1.1, ISS Table 21.2.1, ISS Table 21.3.1, ISS Table 21.4.1, ISS Table 21.5.1, ISS Table 21.6.1, ISS Table 21.7.1 and ISS Table 21.8.1

Table includes data from all phases of Studies 2001, 3001, 3002, 3003, 3004, 3005, 3101 and period 1 of Study 2328.

Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; tx=treatment; ZIP=ziprasidone

7.1.4 Other Search Strategies

No other search strategies were reported.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The following attributes were recorded for all adverse events: onset and resolution dates; severity (mild, moderate, severe and very severe); relationship to study drug (related, unrelated, or not assessable), action taken (none, dose reduction, temporary or permanent stop, hospitalized); and outcome (recovered, not recovered, died).

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 8.1.

Adverse events were collected from baseline (Day 0), defined as the date prior to any treatment, until 30 days after the last dose of study drug. If baseline data were not available, then screening (Day 1) was used as the baseline. Treatment-emergent adverse events were defined as those adverse events that were new in onset or aggravated in severity or frequency after administration of the first dose of study drug through 3 days after the last dose of study drug. If an adverse event had a post-baseline start date and was also present at baseline with the same severity, but with a change in action take (except for 'no action taken'), then it was considered as treatment-emergent. If an adverse event had a post-baseline start date and no action taken, or no change of action from baseline, and was also present at baseline with the same severity, then it was NOT considered as treatment-emergent. If an adverse event had a post-baseline start date, and was present at baseline, but with less severity, it was NOT considered as treatment-emergent. In all cases, only treatment-emergent adverse events will be summarized. Treatment-emergent data have been presented in the text and tables. As multiple study groups were presented, within each study group only adverse events which were newly occurring during the observation time in each of those study groups were tabulated.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor provided a thesaurus for the coding of adverse events. It is unclear if this was the thesaurus used for all studies in the primary safety database (double blind phase of 3000, 3004, 3005, and 3101). This listing was examined to assess the adequacy of coding.

In some instances, similar verbatim terms were coded to separate MedDRA preferred terms. The separate but similar MedDRA preferred terms with clinical significance are listed below and may represent inappropriate splitting of adverse events which may minimize actual adverse event incidences:

1. convulsion, tonic clonic movements[24], grand mal convulsion
2. tachycardia, tachyarrhythmia, sinus tachycardia, heart rate increased
3. bradycardia, sinus bradycardia
4. syncope, syncope vasovagal, loss of consciousness
5. abdominal discomfort, stomach discomfort, dyspepsia
6. sedation, hypersomnia, somnolence
7. proteinuria, protein in urine present
8. extrapyramidal disorder, parkinsonism, parkinsonian rest tremor, tremor (with EPS, extrapyramidal, parkinson, and parkinsonism mentioned in the verbatim term), parkinsonian gait, movement disorder (with EPS, extrapyramidal, or parkinsonism mentioned in the verbatim term), masked facies, difficulty in walking (with parkinsonism mentioned in the verbatim term), cogwheel rigidity, back pain (with parkinsonism mentioned in the verbatim term)
9. pyrexia, body temperature increased
10. hypertension, blood pressure increased
11. orthostatic hypotension, postural orthostatic tachycardia syndrome, blood pressure orthostatic
12. hypotension, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased
13. rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular
14. pruritis, pruritis generalized

In other instances, MedDRA coding may be inappropriate:

1. cholelithiasis to abdominal pain
2. duod ulcer to abdominal pain
3. altered mental status changed secondary to zypreza to adverse drug reaction
4. vaginal fungal inf to aggression
5. hyporexia to bulimia nervosa
6. angina lacunaris to lacunar infarction
7. physical altercation to legal problem
8. verbally assaultive to verbally abused
9. flu, inflamed throat to pharyngeal oedema
10. water retention in ankle to fluid retention
11. giddiness (vertiginous) to dizziness instead of vertigo
12. angina (sore throat), angina (sore throat, respiratory infection) to angina pectoris

[24] Of note, the two verbatim terms coded to this preferred term were generalized tonic clonic convulsion and generalized tonic clonic seizure.

13. generalized tonic clonic convulsion to tonic clonic movements
14. generalized tonic clonic seizure to tonic clonic movements
15. parkinsonism (pains in back) to back pain
16. hypotension (arterial) to orthostatic hypotension
17. arterial hypotension to orthostatic hypotension
18. hypotension with symptom of supine bp 118/54 to orthostatic hypotension
19. tachycardia (post-operative complication-AE per investigator decision) to post procedural complication
20. paroxysmal atrial tachycardia-palpitations coded to palpitations

Most of these inappropriately coded adverse events were rare and not clinically significant. However, the last 8 instances cited are clinically significant.

Also, there was a verbatim term not coded to a MedDRA preferred term (congestion), and there was a preferred term of "heart rate". Additionally, there was some inappropriate coding in the line listing of SAE's provided by the sponsor (e.g., verbatim terms of hearing loss and deafness coded to preferred term of tinnitus).

7.1.5.3 Incidence of common adverse events

Table 7.1.5.3.1 enumerates the incidence of treatment-emergent adverse events that occurred in 5% or more of patients in the double-blind phase of Studies 3000, 3004, 3005, and 3101. Of note, the sponsor did not provide a >2% table in the body of the submission. ≥5% TEAEs with a greater incidence in iloperidone patients than in placebo patients were the following: tachycardia, nausea, dry mouth, dyspepsia, diarrhea, fatigue, headache, dizziness, sedation, somnolence, extrapyramidal disorder, insomnia, agitation, anxiety, schizophrenia, and nasal congestion.

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TABLE 7.1.5.3.1: TREATMENT-EMERGENT ADVERSE EVENTS IN ≥5% OF PATIENTS IN ANY TREATMENT GROUP, SAFETY POPULATION (DOUBLE-BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101)

SOC Preferred Term	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 5-20 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
Total n of TEAEs	*1511*	*1519*	*1472*	*1333*	*4324*	*494*	*888*	*548*
Pts With ≥1 TEAE	*441*	*377*	*378*	*329*	*1084*	*112*	*240*	*130*
	(75.1%)	*(80.2%)*	*(78.3%)*	*(84.1%)*	*(80.7%)*	*(94.9%)*	*(78.4%)*	*(86.7%)*
Cardiac disorders	**15 (2.6%)**	**21 (4.5%)**	**18 (3.7%)**	**46 (11.8%)**	**85 (6.3%)**	**2 (1.7%)**	**5 (1.6%)**	**6 (4.0%)**
Tachycardia	5 (0.9%)	14 (3.0%)	12 (2.5%)	30 (7.7%)	56 (4.2%)	1 (0.8%)	2 (0.7%)	3 (2.0%)
Eye disorders	**25 (4.3%)**	**31 (6.6%)**	**38 (7.9%)**	**20 (5.1%)**	**89 (6.6%)**	**13 (11.0%)**	**22 (7.2%)**	**9 (6.0%)**
Vision Blurred	12 (2.0%)	13 (2.8%)	13 (2.7%)	5 (1.3%)	31 (2.3%)	9 (7.6%)	8 (2.6%)	7 (4.7%)
Gastrointestinal disorders	**191 (32.5%)**	**150 (31.9%)**	**155 (32.1%)**	**150 (38.4%)**	**455 (33.9%)**	**47 (39.8%)**	**105 (34.3%)**	**69 (46.0%)**
Nausea	44 (7.5%)	39 (8.3%)	34 (7.0%)	39 (10.0%)	112 (8.3%)	7 (5.9%)	28 (9.2%)	20 (13.3%)
Dry Mouth	7 (1.2%)	24 (5.1%)	36 (7.5%)	39 (10.0%)	99 (7.4%)	3 (2.5%)	9 (2.9%)	11 (7.3%)
Dyspepsia	39 (6.6%)	36 (7.7%)	26 (5.4%)	29 (7.4%)	91 (6.8%)	13 (11.0%)	18 (5.9%)	15 (10.0%)
Constipation	51 (8.7%)	25 (5.3%)	30 (6.2%)	32 (8.2%)	87 (6.5%)	8 (6.8%)	16 (5.2%)	12 (8.0%)
Diarrhoea	25 (4.3%)	22 (4.7%)	26 (5.4%)	26 (6.6%)	74 (5.5%)	4 (3.4%)	9 (2.9%)	12 (8.0%)
Vomiting	32 (5.5%)	25 (5.3%)	25 (5.2%)	20 (5.1%)	70 (5.2%)	6 (5.1%)	24 (7.8%)	13 (8.7%)
General disorders and administration site conditions	**63 (10.7%)**	**61 (13.0%)**	**66 (13.7%)**	**61 (15.6%)**	**188 (14.0%)**	**18 (15.3%)**	**31 (10.1%)**	**18 (12.0%)**
Fatigue	19 (3.2%)	20 (4.3%)	21 (4.3%)	24 (6.1%)	65 (4.8%)	9 (7.6%)	5 (1.6%)	9 (6.0%)
Musculoskeletal and connective tissue disorders	**83 (14.1%)**	**86 (18.3%)**	**63 (13.0%)**	**70 (17.9%)**	**219 (16.3%)**	**29 (24.6%)**	**36 (11.8%)**	**26 (17.3%)**
Back pain	19 (3.2%)	22 (4.7%)	15 (3.1%)	13 (3.3%)	50 (3.7%)	8 (6.8%)	9 (2.9%)	7 (4.7%)
Pain in extremity	22 (3.7%)	18 (3.8%)	14 (2.9%)	13 (3.3%)	45 (3.3%)	11 (9.3%)	12 (3.9%)	7 (4.7%)
Nervous system disorders	**207 (35.3%)**	**211 (44.9%)**	**196 (40.6%)**	**185 (47.3%)**	**592 (44.0%)**	**83 (70.3%)**	**145 (47.4%)**	**94 (62.7%)**
Headache	117(19.9%)	114 (24.3%)	92 (19.0%)	74 (18.9%)	280 (20.8%)	29 (24.6%)	59 (19.3%)	34 (22.7%)
Dizziness	41 (7.0%)	56 (11.9%)	50 (10.4%)	77 (19.7%)	183 (13.6%)	6 (5.1%)	22 (7.2%)	20 (13.3%)
Sedation	18 (3.1%)	19 (4.0%)	19 (3.9%)	40 (10.2%)	78 (5.8%)	3 (2.5%)	13 (4.2%)	41 (27.3%)

SOC Preferred Term	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 5-20 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
Nervous system disorders (cont'd)								
Somnolence	14 (2.4%)	23 (4.9%)	26 (5.4%)	22 (5.6%)	71 (5.3%)	8 (6.8%)	18 (5.9%)	9 (6.0%)
Extrapyramidal disorder	24 (4.1%)	25 (5.3%)	22 (4.6%)	15 (3.8%)	62 (4.6%)	24 (20.3%)	29 (9.5%)	14 (9.3%)
Tremor	11 (1.9%)	13 (2.8%)	12 (2.5%)	12 (3.1%)	37 (2.8%)	26 (22.0%)	21 (6.9%)	6 (4.0%)
Akathisia	16 (2.7%)	17 (3.6%)	8 (1.7%)	9 (2.3%)	34 (2.5%)	16 (13.6%)	21 (6.9%)	11 (7.3%)
Psychiatric disorders	**233 (39.7%)**	**211 (44.9%)**	**207 (42.9%)**	**93 (23.8%)**	**511 (38.0%)**	**67 (56.8%)**	**119 (38.9%)**	**41 (27.3%)**
Insomnia	105(17.9%)	85 (18.1%)	87 (18.0%)	29 (7.4%)	201 (15.0%)	31 (26.3%)	44 (14.4%)	9 (6.0%)
Agitation	87 (14.8%)	91 (19.4%)	57 (11.8%)	13 (3.3%)	161 (12.0%)	28 (23.7%)	29 (9.5%)	10 (6.7%)
Anxiety	64 (10.9%)	64 (13.6%)	51 (10.6%)	18 (4.6%)	133 (9.9%)	25 (21.2%)	38 (12.4%)	7 (4.7%)
Restlessness	24 (4.1%)	14 (3.0%)	17 (3.5%)	14 (3.6%)	45 (3.3%)	11 (9.3%)	21 (6.9%)	8 (5.3%)
Schizophrenia	24 (4.1%)	10 (2.1%)	26 (5.4%)	9 (2.3%)	45 (3.3%)	3 (2.5%)	8 (2.6%)	1 (0.7%)
Psychotic disorder	16 (2.7%)	12 (2.6%)	18 (3.7%)	7 (1.8%)	37 (2.8%)	6 (5.1%)	3 (1.0%)	3 (2.0%)
Respiratory disorders	**46 (7.8%)**	**59 (12.6%)**	**66 (13.7%)**	**64 (16.4%)**	**189 (14.1%)**	**12 (10.2%)**	**28 (9.2%)**	**20 (13.3%)**
Nasal congestion	14 (2.4%)	22 (4.7%)	24 (5.0%)	31 (7.9%)	77 (5.7%)	2 (1.7%)	8 (2.6%)	5 (3.3%)

Data Source: ISS Table 6.1.2
Table includes data from double-blind phase of Studies 3000, 3004, 3005 and 3101.
HAL=haloperidol; ILO comb.=combined iloperidone; RIS=risperidone; TEAE=treatment-emergent adverse event; ZIP=ziprasidone.
Patients who experienced multiple AEs within the same SOC were counted only once for that same SOC.
Patients who experienced the same AE multiple times within the same SOC were counted only once for the corresponding Preferred Term.
Adverse events are sorted alphabetically by SOC and within each SOC the preferred term is presented by decreasing order of frequency in the combined iloperidone group.
Percentages are based on the total number of patients within each treatment/dose group.

7.1.5.4 Common adverse event tables

Please see Section 7.1.5.3.

7.1.5.5 Identifying common and drug-related adverse events

Adverse events that are considered common and drug-related (i.e., reported in at least 5% in iloperidone patients at a rate at least twice that in the placebo group) are: tachycardia, dry mouth, dizziness, sedation, somnolence, and nasal congestion.

7.1.5.6 Additional analyses and explorations

Demographic Effects on Adverse Event Incidence
The sponsor did not perform subgroup analyses of demographic variables (age 6-9 or 10-12, gender, and race white or nonwhite) on the reporting rates of the above common, drug related events.

Dose-Relatedness
There appears to be a dose-related trend for treatment-emergent adverse events of dry mouth, somnolence and nasal congestion. For all other adverse events there does not appear to be a dose response or it is unclear.

7.1.6 Less Common Adverse Events

The sponsor did not provide a listing of all adverse events in all studies for inspection for adverse events that could be considered serious adverse events but were not already classified as serious.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Blood samples for complete blood count with differential and serum biochemistry were taken at baseline and reassessed during and at the end of treatment. The sponsor did not describe urinalysis procedures.

7.1.7.2 Standard analyses and explorations of laboratory data

7.1.7.2.1 Analyses focused on measures of central tendency

Mean Change from Baseline to Endpoint in Laboratory Tests
Mean changes from baseline were computed for several laboratory variables[25] for the double-blind phase of Study 3000, 3004, 3005, and 3101. Results are displayed in ISS Tables 12.1.2 and 13.1.2.

For the double-blind phase of Study 3000, 3004, 3005, and 3101, mean changes from baseline to final visit assessment were statistically significantly different between iloperidone and placebo for the lab values presented in Table 7.1.7.2.1.1 below.[26]

TABLE 7.1.7.2.1.1: MEAN CHANGES FROM BASELINE TO ENDPOINT FOR SELECT SERUM LABORATORY TESTS (DOUBLE-BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101)

	Placebo		Ilo 4-8 mg/d		Ilo 10-16 mg/d		Ilo 20-24 mg/d	
	N	LS Mean Δ	N	LS Mean Δ	N	LS Mean Δ	N	LS Mean Δ
Basophils (10^9/L)	532	0.0	403	0.0	454	-0.0	372	-0.0*
Basophils (%)	534	-0.0	403	0.0*	454	-0.0	372	-0.1*
Eosinophils (10^9/L)	532	-0.0	403	-0.0*	454	-0.0*	372	-0.0
Hgb (g/L)	533	1.2	403	-1.9*	454	-2.3*	372	-2.1*
Hct (1/L)	529	0.0	400	-0.0*	451	-0.0*	372	-0.0*
Lymphocytes (10^9/L)	532	0.0	403	-0.1*	454	-0.2*	372	-0.2*
Lymphocytes (%)	534	0.1	403	-0.4	454	-1.2*	372	-1.0*
Monocytes (10^9/L)	532	-0.0	403	0.0	454	-0.0	372	-0.1*
Monocytes (%)	534	-0.4	403	0.2*	454	-0.3	372	-0.2

[25] Basophils, basophils %, eosinophils, eosinophils %, Hgb, Hct, lymphocytes, lymphocytes %, monocytes, monocytes %, neutrophils segs, neutrophils segs %, neutrophils total, neutrophils total %, platelet count, RBC, WBC, albumin, alkaline phosphatase, total bilirubin, direct bilirubin, AST, ALT, BUN, creatinine, total cholesterol, creatinine phosphokinase, globulin, glucose, glycohemoglobin A1C, HDL, LDH, LDL, prolactin, triglycerides, TSH, uric acid, calcium, chloride, bicarbonate, inorganic phosphorus, magnesium, potassium, and sodium
[26] Changes for other variables were not significantly different between drug and placebo.

Neutrophils (Segs, %)	136	-0.6	2	11.1*	19	2.4	258	1.4*
Neutrophils (Total, 10^9/L)	398	0.2	401	-0.5*	435	-0.1	114	-0.3
Platelets (10^9/L)	528	9.5	398	-1.8*	451	0.4*	372	-1.9*
RBC (10^9/L)	533	0.1	403	-0.1*	454	-0.1*	372	-0.0*
WBC (10^9/L)	533	0.1	402	-0.5*	454	-0.2*	372	-0.4*
Albumin (g/L)	539	0.7	407	-0.6*	458	-0.4*	375	0.3
Alkaline Phosphatase (u/L)	539	-2.2	404	-4.7*	457	-3.6*	376	-4.4*
Total Bilirubin (umol/L)	509	0.7	388	-0.2*	419	-0.4*	363	0.2
BUN (mmol/L)	541	0.1	407	-0.1*	458	0.1	376	-0.1*
Calcium (mmol/L)	541	0.0	407	-0.0*	457	-0.0*	376	0.0*
Total Cholesterol (mmol/L)	541	-0.1	407	-0.2	458	-0.2	376	0.5*
Chloride (mmol/L)	541	0.1	407	-0.1	457	-0.0	376	0.9*
Bicarbonate (mmol/L)	539	-0.0	407	0.5*	458	0.0	375	-0.9*
Glucose (mmol/L)	538	-0.1	404	0.6*	455	0.8*	373	0.2
HDL (mmol/L)	138	-0.1	2	0.1	19	0.0	259	0.0*
Inorganic Phosphorus (mmol/L)	538	-0.0	401	-0.0	454	-0.0	375	0.0*
LDL (mmol/L)	135	0.0	2	0.4	18	-0.1	248	0.2*
Magnesium (mmol/L)	403	0.0	405	-0.0*	438	-0.0*	117	-0.0*
Potassium (mmol/L)	538	-0.0	401	-0.1	453	-0.1*	374	0.0
Total Protein (g/L)	541	0.9	407	-0.7*	458	-0.7*	376	-0.5*

Sodium (mmol/L)	541	-0.1	407	-0.1	457	0.2*	376	-0.0
Triglycerides (mmol/L)	541	-0.3	407	-0.3	457	-0.3	376	-0.0*
Uric Acid (umol/L)	541	18.6	407	43.1*	458	40.7*	376	18.8

*p-value < 0.05 from ANCOVA analysis comparing dose groups on change from baseline, controlling for baseline

Of note, the sponsor did not provide an ANCOVA analysis using a p-value of < 0.10, which is more appropriate for safety analyses.

With the exception of neutrophils (segs, %), all of these mean changes were small and unlikely to be clinically significant. The mean change in neutrophils (segs, %) in the Ilo 4-8 mg/d group was large, though, due to a sample size of only 2, its clinical significance is unclear.

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially Clinically Significant Laboratory Changes
Criteria for potentially clinically important (PCI) laboratory test results are displayed in Appendix 10.5.3 in Section 10.5. The proportions of patients who met these criteria for the double-blind phase of Studies 3000, 3004, 3005, and 3101 were extracted from the sponsor's 1/4/08 submission and displayed in Appendix 10.5.4 in Section 10.5. Please note that the analyses for serum hematology and chemistry laboratory results are based on worst value observed during the treatment period.

The proportions of patients with PCI results were noticeably greater in the iloperidone groups than in the placebo group for the laboratory parameters listed in the table below. All these laboratory parameters had at least one iloperidone dose group with a risk ratio of > 1 and with a confidence interval excluding 1. These risk ratios are indicated in bold font.

TABLE 7.1.7.2.2.1: INCIDENCE OF SELECT POTENTIALLY CLINICALLY IMPORTANT LABORATORY VALUES (DOUBLE-BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101)							
	Placebo	**Ilo 4-8 mg/d**		**Ilo 10-16 mg/d**		**Ilo 20-24 mg/d**	
	Prop	Prop	RR (95% CI)	Prop	RR (95% CI)	Prop	RR (95% CI)
Low Hgb	8% (45/533)	10% (42/403)	1.23 (0.83 to 1.84)	13% (57/451)	**1.50** (1.03 to 2.17)	23% (85/372)	**2.71** (1.93 to 3.79)
Low Hct	6% (30/529)	10% (39/400)	1.57 (0.99 to 2.48)	13% (57/451)	**2.23** (1.46 to 3.40)	18% (69/372)	**3.27** (2.18 to 4.92)
Low RBC	9% (46/587)	19% (76/403)	**2.41** (1.71 to 3.39)	21% (94/454)	**2.64** (1.90 to 3.68)	17% (63/372)	**2.16** (1.51 to 3.09)
Low BUN	3% (16/541)	1% (4/407)	0.33 (0.11 to 0.99)	1% (4/458)	0.30 (0.10 to 0.88)	7% (25/376)	**2.25** (1.22 to 4.15)
High Prolactin	12% (39/333)	28% (81/289)	**2.39** (1.69 to 3.39)	37% (76/206)	**3.15** (2.23 to 4.45)	26% (63/247)	**2.18** (1.51 to 3.13)
Low Calcium	1% (7/541)	7% (28/407)	**5.32** (2.35 to 12.05)	3% (13/457)	2.20 (0.88 to 5.46)	1% (3/376)	0.62 (0.16 to 2.37)
High Chloride	2% (13/541)	0% (2/407)	0.20 (0.05 to 0.90)	1% (4/458)	0.36 (0.12 to 1.10)	8% (30/376)	**3.32** (1.76 to 6.28)
High inorganic phosphorus	6% (35/538)	4% (17/401)	0.65 (0.37 to 1.15)	3% (14/454)	0.47 (0.26 to 0.87)	14% (53/376)	**2.17** (1.44 to 3.25)
Urine Red Blood Cells Post-Baseline	16% (30/184)	44% (10/23)	**2.67** (1.51 to 4.71)	34% (26/76)	**2.10** (1.34 to 3.30)	6% (17/283)	0.37 (0.21 to 0.65)
Urine Red Blood Cells Change from BL	11% (20/184)	22% (5/23)	2.00 (0.83 to 4.82)	13% (10/76)	1.21 (0.59 to 2.46)	3% (8/283)	0.26 (0.12 to 0.58)

Prop=Proportion
RR=Risk Ratio
Source: Reviewer's analysis

The finding of low Hgb, low Hct, and low RBC appears dose related and is clinically significant. Also significant is the finding of high prolactin. The sponsor did not provide minimum and maximum laboratory values for this study population.

The clinical significance of a low BUN without other indications of malnutrition is unclear. The clinical significance of low calcium in the lowest dose group is unclear. The clinical significance of high chloride and high inorganic phosphorus in the highest dose group without other major indications of renal dysfunction is unclear. The clinical significance of urine red blood cells only in the post-baseline analysis and only in the 2 lower dose groups is unclear.

7.1.7.2.3 Marked outliers and dropouts for laboratory abnormalities

Dropouts due to Laboratory Abnormalities
The sponsor did not provide data on dropouts due to laboratory abnormalities.

7.1.7.3 Additional analyses and explorations

No additional explorations were performed.

7.1.7.4 Special assessments

No special assessments which would significantly impact on the safety profile of this drug were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The sponsor did not describe vital signs testing procedures.

7.1.8.2 Standard analyses and explorations of vital signs data

7.1.8.2.1 Analyses focused on measures of central tendencies

Mean Change from Baseline in Vital Sign Measures
Mean changes from baseline were computed for supine SBP, 3 minute standing SBP, supine DBP, 3 minute standing DBP, supine pulse rate, 3 minute standing pulse rate, weight, and body temperature for the double-blind phase of Study 3000, 3004, 3005, and 3101. Results are displayed in ISS Tables 15.1.2 and 16.1.2.

For the double-blind phase of Study 3000, 3004, 3005, and 3101, mean changes from baseline to final visit assessment were statistically significantly different between iloperidone and placebo for the vital sign measures presented in Table 7.1.8.2.1.1 below.[27]

TABLE 7.1.8.2.1.1: MEAN CHANGES FROM BASELINE TO ENDPOINT FOR VITAL SIGN MEASURES (DOUBLE-BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101)

	Placebo		Ilo 4-8 mg/d		Ilo 10-16 mg/d		Ilo 20-24 mg/d	
	N	LS Mean Δ	N	LS Mean Δ	N	LS Mean Δ	N	LS Mean Δ
Supine SBP (mm Hg)	580	0.9	460	-1.1*	479	-1.3*	391	-1.9*
Standing SBP (mm Hg)	580	-0.0	459	-4.7*	479	-4.4*	391	-5.1*
Supine DBP (mm Hg)	580	0.3	460	-1.9*	479	-0.8*	391	-1.3*
Standing DBP (mm Hg)	580	-0.0	459	-4.2*	479	-4.2*	391	-4.7*
Supine Pulse Rate (bpm)	580	0.7	460	2.5*	479	0.9	391	2.3*
Standing Pulse Rate (bpm)	580	0.5	459	5.6*	478	3.2*	391	7.3*
Weight (kg)	579	-0.1	455	1.5*	481	2.0*	391	2.7*
Body Temperature (°C)	579	0.0	460	-0.0	480	-0.1*	391	-0.1*

*p-value < 0.05 from ANCOVA analysis comparing dose groups on change from baseline, controlling for baseline

Of note, the sponsor did not provide an ANCOVA analysis using a p-value of < 0.10, which is more appropriate for safety analyses.

The mean change in supine SBP, supine DBP, supine pulse rate, standing pulse rate, and body temperature were small and unlikely to be clinically significant. The mean changes in standing SBP and standing DBP, appear clinically significant, even though their magnitudes do not meet the technical definition of orthostatic hypotension. The mean change in weight appears clinically significant.

[27] Changes for other variables were not significantly different between drug and placebo.

7.1.8.2.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially Clinically Significant Vital Sign Changes
Criteria for potentially clinically important (PCI) vital sign results are displayed in Appendix 10.5.5 in Section 10.5. The proportions of patients who met these criteria for the double-blind phase of Studies 3000, 3004, 3005, and 3101 were extracted from the sponsor's 1/4/08 submission and are displayed in Appendix 10.5.6 in Section 10.5.

The proportions of patients with PCI results were noticeably greater in the iloperidone groups than in the placebo group for the vital sign parameters listed in the table below. All these vital sign parameters had a risk ratio of > 1 and with a confidence interval excluding 1 for all dose groups.

TABLE 7.1.8.3.2.1: INCIDENCE OF SELECT POTENTIALLY CLINICALLY IMPORTANT VITAL SIGN VALUES (DOUBLE-BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101)

	Placebo	**Ilo 4-8 mg/d**		**Ilo 10-16 mg/d**		**Ilo 20-24 mg/d**	
	Prop	Prop	RR (95% CI)	Prop	RR (95% CI)	Prop	RR (95% CI)
Pulse Rate ≥ 120 bpm	8% (49/581)	34% (156/460)	**4.02** (2.99 to 5.41)	25% (120/480)	**2.96** (2.18 to 4.04)	36% (142/391)	**4.31** (3.20 to 5.80)
Pulse Rate Increase ≥ 15 bpm	52% (303/581)	75% (344/460)	**1.43** (1.30 to 1.58)	64% (307/480)	**1.23** (1.11 to 1.36)	71% (277/391)	**1.36** (1.23 to 1.50)
SBP ≤ 90 mm Hg	10% (58/581)	24% (112/460)	**2.44** (1.82 to 3.27)	20% (95/480)	**1.98** (1.46 to 2.68)	17% (67/391)	**1.72** (1.24 to 2.38)
Weight Increase ≥ 7%	4% (25/587)	11% (49/470)	**2.45** (1.54 to 3.90)	12% (58/483)	**2.82** (1.79 to 4.44)	18% (72/391)	**4.32** (2.79 to 6.69)

Source: Reviewer's analysis

All of the above findings are clinically significant. The sponsor did not provide minimum and maximum vital signs values for this study population.

7.1.8.2.3 Marked outliers and dropouts for vital sign abnormalities

Dropouts due to Vital Sign or Weight Abnormalities
The sponsor did not provide data on dropouts due to vital sign abnormalities.

7.1.8.3 Additional analyses and explorations

No further explorations were deemed necessary.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG's for "most" patients were recorded throughout the study. The sponsor did not provide more detailed information regarding ECG monitoring.

In preclinical trials[28], two in vitro investigations showed that iloperidone had the potential to prolong the QT interval as assessed by (1) effects on isolated dog Purkinje fiber firing and (2) human ether-a-go-go-related gene (hERG) ion channel currents in cloned cell lines. Iloperidone was also found to have hypotensive and vasodilatory effects in rats and dogs. The hypotensive activity of iloperidone was also supported by its preferential affinity for α_1 over α_2 adrenergic receptors in vitro. Except for a transient increase in heart rate observed in some studies, no other notable pulmonary or hemodynamic effects (e.g., cardiac output changes or ECG findings) were reported in rats or dogs.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Mean Change from Baseline in ECG parameters
For the double-blind phase of Studies 3000, 3004, 3005, and 3101, mean changes from baseline to final on-therapy assessment were computed for the parameters of heart rate; QTc, PR, QRS, and RR intervals for iloperidone and placebo treatment groups. Results are displayed in ISS Table 17.7.2.

[28] Per a 5/15/08 email from Sonia Tabacove, Ph.D., Pharm/Tox Reviewer

Of note, the sponsor did not perform statistical testing on mean change from baseline data for heart rate, PR interval, QRS interval, and RR interval. For QTcF and QTcB, mean changes from baseline to endpoint were statistically significantly different between iloperidone and placebo for all dose groups. Data are presented in Table 7.1.9.3.1.1 below.

TABLE 7.1.9.3.1.1: MEAN CHANGES FROM BASELINE TO ENDPOINT FOR QTC (DOUBLE-BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101)

	Placebo		Ilo 4-8 mg/d		Ilo 10-16 mg/d		Ilo 20-24 mg/d	
	N	LS Mean Δ	N	LS Mean Δ	N	LS Mean Δ	N	LS Mean Δ
Fridericia's Formula (msec)	542	-0.6	400	2.5*	445	3.5*	375	8.7*
Bazett's Formula (msec)	542	-0.2	400	4.8*	445	4.3*	375	12.1*

The drug/placebo differences are clinically significant and appear dose related.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially Clinically Significant ECG Changes
Criteria for potentially clinically important (PCI) ECG results are displayed in Appendix 10.5.7 in Section 10.5. Of note, these criteria do not include a criterion for rhythm change. The proportions of patients who met these criteria for the double-blind phase of Studies 3000, 3004, 3005, and 3101 were extracted from the sponsor's 11/27/07 and 1/4/08 submissions and are displayed in Appendix 10.5.8 in Section 10.5.

The proportions of PCI results were comparable between the iloperidone groups and placebo group for heart rate, PR interval, and QRS interval. For a QTcF $\geq$ 450 msec, proportions were 2% (18/470) in the iloperidone 4-8 mg/d group [RR=**3.75** (95% CI=1.50 to 9.36)], 2% (34/483) in the iloperidone 10-16 mg/d group [RR=**6.89** (95% CI=2.92 to 16.3)], 4% (17/391) in the iloperidone 20-24 mg/d group [RR=**4.25** (95% CI=1.69 to 10.69)] and 1% (6/587) in the placebo group.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Dropouts due to ECG Abnormalities
The sponsor did not provide data on dropouts due to ECG abnormalities.

7.1.9.4 Additional analyses and explorations

No ECG parameters warranted additional exploration.

7.1.10 Immunogenicity

No immunogenicity studies were performed.

7.1.11 Human Carcinogenicity

No carcinogenicity study data was submitted with this application.

7.1.12 Special Safety Studies

The sponsor performed a thorough QT study (Study 2328) which was reviewed in detail by the QT team. The results of this study are summarized in Table 7.1.12.1 below, extracted from the sponsor's submission.

TABLE 7.1.12.1: MEAN QTC CHANGE FROM BASELINE TO STEADY STATE AT TMAX DURING TREATMENT PERIODS 1, 2, AND 3, STUDY 2328

	ILO 8 mg BID	ILO 12 mg BID	ILO 24 mg QD	ZIP 80 mg BID	QUE 375 mg BID
Treatment Period 1					
Inhibitor	None	None	None	None	None
N	29	34	31	33	33
Mean (Fridericia)	8.9±10.5	9.0±12.5	15.4±11.7	9.9±11.0	1.3±11.1
Mean (Bazett)	16.0±13.5	15.6±13.9	19.3±14.8	14.6±12.7	12.6±14.2
Treatment Period 2					
Inhibitor	CYP2D6 [a]	CYP2D6 [a]	CYP2D6 [a]	CYP3A4 [b]	CYP3A4 [b]
N	26	31	31	30	32
Mean (Fridericia)	11.2±12.0	11.6±16.8	17.5±10.3	15.9±11.8	2.6±11.5
Mean (Bazett)	11.4±14.0	7.5±17.8	15.0±11.9	21.0±13.9	17.2±15.5
Treatment Period 3					
Inhibitor	CYP2D6 [a] + CYP3A4 [b]	CYP2D6 [a] + CYP3A4 [b]	CYP2D6 [a] + CYP3A4 [b]	-	-
N	25	30	29	-	-
Mean (Fridericia)	15.7±14.1	19.3±17.1	19.5±11.9	-	-
Mean (Bazett)	15.9±14.5	15.8±17.9	17.0±13.9	-	-

Data Source: ILO522 2328\Table 9-2
ILO=iloperidone; N=number of patients; QUE=quetiapine; ZIP=ziprasidone
Patients assigned to ZIP or QUE treatment did not have a Period 3 assessment.
[a] Paroxetine 20 mg QD was used as a CYP2D6 inhibitor.
[b] Ketoconazole 200 mg BID was used as a CYP3A4 inhibitor.
*T_{max}=estimated time of maximum concentration (ILO=2-4 hours postdose; ZIP=5-7 hours postdose; QUE=1 to 2.5 hours postdose)

7.1.13 Withdrawal Phenomena and/or Abuse Potential

In clinical studies, a dose tapering strategy was not used. There were no reported instances of withdrawal effects after abrupt discontinuation of iloperidone.

Iloperidone has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence.

7.1.14 Human Reproduction and Pregnancy Data

There were no studies in this submission designed specifically to assess safety in human reproduction and pregnancy.

During the clinical development of iloperidone, 5 pregnancies were reported in patients treated with iloperidone. Two were ectopic pregnancies, both resulting in abortions and complete recovery of the patients. Two resulted in the birth of normal, healthy infants. A fifth pregnancy resulted in a spontaneous abortion during the seventh to ninth week of gestation. The pregnancies are summarized in the table below.

Study No. Pt. ID	Maternal Age/Race	ILO Dose (mg/d)	ILO Duration of Tx (days)	Study Day of Positive Pregnancy Test	Action Taken	Outcome	Comments
3000							
559 1021	35/Black	8-16	264	265[a]	none	birth of healthy baby	
3001							
093 1004	37/White	2	2	2	tx dc	abortion	extrauterine pregnancy
010 1009	28/White	8	184	182	end d-b phase	birth of healthy baby	
047-1007	35/White	16	117[b]	101	tx dc	spontaneous abortion (estimated Week 7 to 9 of pregnancy)	event occurred on Study Day 112; patient dc'd study drug on unspecified date without notifying the investigator
3005							
509 1004	35/Black	10	397	394	tx dc	abortion	ectopic pregnancy

Data Source: ISS Appendix 6
d-b=double blind; dc=discontinuation; tx=treatment
[a] One day posttreatment
[b] Last known dose of study drug taken on Study Day 92; patient withdrawn from the study on Day 117 for protocol violation.

7.1.15 Assessment of Effect on Growth

The effect on growth was not assessed in these trials, which were conducted in adult patients.

7.1.16 Overdose Experience

In clinical studies, including only the short-term phase of Study 3101, there were 8 reports of iloperidone overdose. Adverse events associated with overdose were dizziness, incoherent/slurred speech, difficulty walking rigidity, gastritis, hypokalemia, loss of consciousness, tachycardia, hypotension, vertigo and QTcF interval >500 msec (507 msec). The

patient who experienced loss of consciousness took 20 capsules of iloperidone and ten to twenty 7.5-mg tablets of zopiclone. Incidences of overdose are summarized in the table below, extracted from the sponsor's submission.

Study Number/ Patient ID	Age/ Sex/ Race	Assigned ILO Dose (mg/d)	ILO Duration of Tx	Study Day of Overdose	Overdose Amount	AEs Associated With Overdose	Action Taken	Outcome	Comments
ILP3000									
541-1013	49/F/Black	12	42	D14 to D20	4 tabs/d rather than 2 tabs/d	None	None	Resolved	Pt given double dose of study med (medication error)
ILP3002									
015 1007	25/F/Asian	16	364	308	19 tabs 152 mg	Dizziness	Hospitalized Study drug temp stop (3 days)	Recovered	Suicide attempt
054 1025	33/F/Asian	12	20	20	15 caps 90 mg	None	Hospitalized Study drug dc'd	Recovered	Suicide attempt
072 1008	29/M/Asian	12	364	249	48 caps 288 mg	None	Study drug temp stop (18 days)	Recovered	Overdosed while under the influence of auditory hallucinational symptoms
072 1035	28/M/Asian	12	148 (O-L)	O-L 31	73 tabs over 4 days 438 mg	Incoherent/ slurred speech, difficulty walking, rigidity	Hospitalized	Recovered	QTc >500 after overdose
ILP3003									
625 1021	25/F/Asian	12	259	256	2-3 12-18 mg	Gastritis, hypokalemia	Hospitalized Study drug dc'd		Suicide attempt
ILP3004									
706 1019	36/M/White	4	469	277	20 caps 40 mg	Loss of consciousness	Hospitalized	Recovered	Zopiclone (10 tabs to 20 tabs, 7.5 mg/tab) also taken as part of overdose
ILP3005									
941 1002	36/F/White	8	136 (O-L)	O-L 136	34 tabs 136 mg	Tachycardia, hypotension, vertigo	Hospitalized Study drug dc'd	Recovered	

Source Data: ISS Appendix 7.
AE = adverse event; caps = capsules; d = day; dc = discontinuation; F = female; ID = identification; ILO = iloperidone; M = male; O-L = open-label; Pt = patient; tabs = tablets; temp = temporarily; Tx = treatment.
Note: ISS Appendix 7 indicates there are 27 overdoses; only those overdoses associated with iloperidone treatment are presented in this table.

7.1.17 Postmarketing Experience

Iloperidone has not been approved or marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

See Section 4.2.

7.2.1.2 Demographics

TABLE 7.2.1.2.1: DEMOGRAPHICS AND BASELINE CHARACTERISTICS, DOUBLE-BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101 (SAFETY POPULATION)[29]

Patient Characteristics	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 5-20 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
Sex								
Male	399 (68.0%)	337 (71.7%)	319 (66.0%)	302 (77.2%)	958 (71.3%)	79 (66.9%)	209 (68.3%)	113 (75.3%)
Female	188 (32.0%)	133 (28.3%)	164 (34.0%)	89 (22.8%)	386 (28.7%)	39 (33.1%)	97 (31.7%)	37 (24.7%)
Age (years)								
n	587	470	483	391	1344	118	306	150
Mean	39.5	37.6	39.7	39.1	38.8	39.3	38.7	40.1
SD	10.30	10.02	10.41	10.60	10.36	9.47	11.22	10.02
Median	40.0	38.0	40.0	40.0	39.0	40.0	38.5	41.0
Minimum	18	18	18	18	18	19	17	20
Maximum	69	68	68	65	68	59	67	63
Age (age categories)								
< 50 Years	500 (85.2%)	420 (89.4%)	390 (80.7%)	329 (84.1%)	1139 (84.7%)	100 (84.7%)	248 (81.0%)	124 (82.7%)
≥ 50 Years	87 (14.8%)	50 (10.6%)	93 (19.3%)	62 (15.9%)	205 (15.3%)	18 (15.3%)	58 (19.0%)	26 (17.3%)
Race								
Asian	19 (3.2%)	11 (2.3%)	10 (2.1%)	26 (6.6%)	47 (3.5%)	3 (2.5%)	3 (1.0%)	12 (8.0%)
Black/African American	222 (37.8%)	188 (40.0%)	143 (29.6%)	161 (41.2%)	492 (36.6%)	53 (44.9%)	77 (25.2%)	77 (51.3%)
White	306 (52.1%)	237 (50.4%)	301 (62.3%)	188 (48.1%)	726 (54.0%)	55 (46.6%)	208 (68.0%)	51 (34.0%)
Other	40 (6.8%)	34 (7.2%)	29 (6.0%)	16 (4.1%)	79 (5.9%)	7 (5.9%)	18 (5.9%)	10 (6.7%)
Age psychosis was diagnosed (years)								
< 18	104 (17.7%)	104 (22.1%)	78 (16.1%)	64 (16.4%)	246 (18.3%)	23 (19.5%)	51 (16.7%)	25 (16.7%)
18-24	253 (43.1%)	183 (38.9%)	187 (38.7%)	166 (42.5%)	536 (39.9%)	54 (45.8%)	125 (40.8%)	56 (37.3%)
25-44	201 (34.2%)	170 (36.2%)	202 (41.8%)	149 (38.1%)	521 (38.8%)	37 (31.4%)	119 (38.9%)	65 (43.3%)
45-65	19 (3.2%)	6 (1.3%)	13 (2.7%)	8 (2.0%)	27 (2.0%)	1 (0.8%)	9 (2.9%)	2 (1.3%)
Missing	10 (1.7%)	7 (1.5%)	3 (0.6%)	4 (1.0%)	14 (1.0%)	3 (2.5%)	2 (0.7%)	2 (1.3%)
Previous hospitalization for psychosis								
Yes	564 (96.1%)	446 (94.9%)	451 (93.4%)	358 (91.6%)	1255 (93.4%)	115 (97.5%)	283 (92.5%)	134 (89.3%)
No	20 (3.4%)	23 (4.9%)	31 (6.4%)	30 (7.7%)	84 (6.3%)	3 (2.5%)	23 (7.5%)	12 (8.0%)
Unknown	3 (0.5%)	1 (0.2%)	1 (0.2%)	3 (0.8%)	5 (0.4%)	0	0	4 (2.7%)

Characteristics	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 5-20 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
Number of previous hospitalizations for psychosis								
1 - 5	263 (46.6%)	193 (43.3%)	221 (49.0%)	161 (45.0%)	575 (45.8%)	41 (35.7%)	138 (48.8%)	60 (44.8%)
6 - 10	129 (22.9%)	138 (30.9%)	117 (25.9%)	93 (26.0%)	348 (27.7%)	35 (30.4%)	70 (24.7%)	34 (25.4%)
11 - 15	85 (15.1%)	50 (11.2%)	57 (12.6%)	49 (13.7%)	156 (12.4%)	14 (12.2%)	38 (13.4%)	16 (11.9%)
16 or more	86 (15.2%)	62 (13.9%)	54 (12.0%)	55 (15.4%)	171 (13.6%)	25 (21.7%)	37 (13.1%)	24 (17.9%)
Missing	1 (0.2%)	3 (0.7%)	2 (0.4%)	0	5 (0.4%)	0	0	0
DSM-IV classification of schizophrenia								
10 (Disorganized)	23 (3.9%)	26 (5.5%)	19 (3.9%)	21 (5.4%)	66 (4.9%)	2 (1.7%)	16 (5.2%)	3 (2.0%)
30 (Paranoid)	391 (66.6%)	270 (57.4%)	303 (62.7%)	300 (76.7%)	873 (65.0%)	59 (50.0%)	185 (60.5%)	127 (84.7%)
60 (Residual)	0	0	1 (0.2%)	0	1 (0.1%)	0	0	0
90 (Undifferentiated)	53 (9.0%)	58 (12.3%)	58 (12.0%)	45 (11.5%)	161 (12.0%)	12 (10.2%)	36 (11.8%)	20 (13.3%)
70 (Schizoaffective)	120 (20.4%)	115 (24.5%)	102 (21.1%)	25 (6.4%)	242 (18.0%)	45 (38.1%)	69 (22.5%)	0
Missing	0	1 (0.2%)	0	0	1 (0.1%)	0	0	0

Data Source: ISS Table.1.1.2
Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.
Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone
Percentages are based on the total number of patients within treatment/dose group.
Percentages may not add to 100% due to missing data and/or rounding.

[29] Of note, the sponsor did not provide this information for the pool of all iloperidone studies.

7.2.1.3 Extent of exposure (dose/duration)

The sponsor provided a table presenting the overall exposure for 9 of the 38 iloperidone studies.[30] This table is extracted from the sponsor's 1/23/08 120-day Safety Update and included below. Of note, the table describes duration of treatment by assigned treatment group and does not describe mean daily dose.

APPEARS THIS WAY ON ORIGINAL

[30] The sponsor states that 27 of the 29 remaining studies were mostly single-dose or short-term studies, and do not contribute substantially to the overall cumulative extent of exposure.

TABLE 7.2.1.3.1: DURATION OF TREATMENT, STUDIES 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101, AND 2328

Duration of Treatment Time period	Placebo (N = 587)	ILO 4-8 mg/d (N = 1227)	ILO 10-16 mg/d (N = 1562)	ILO 20-24 mg/d (N =508)	ILO Total (N = 3297)	HAL 5-20 mg/d (N = 546)	RIS 4-8 mg/d (N = 311)	ZIP 160 mg/d (N = 184)
Mean (±SD), days	26.0 (13.71)	209.5 (294.73)	293.4 (317.14)	80.6 (123.39)	229.4 (296.29)	175.0 (155.92)	66.1 (87.84)	20.0 (9.16)
Cumulative duration of treatment:								
>1 Week	507 (86.4%)	1006 (82.0%)	1521 (97.4%)	499 (98.2%)	3026 (91.8%)	499 (91.4%)	285 (91.6%)	168 (91.3%)
>2 Weeks	422 (71.9%)	902 (73.5%)	1436 (91.9%)	440 (86.6%)	2778(84.3%)	460 (84.2%)	251 (80.7%)	111 (60.3%)
>3 Weeks	364 (62.0%)	822 (67.0%)	1361 (87.1%)	339 (66.7%)	2522 (76.5%)	428 (78.4%)	234 (75.2%)	102 (55.4%)
>4 Weeks	225 (38.3%)	769 (62.7%)	1313 (84.1%)	214 (42.1%)	2296 (69.6%)	408 (74.7%)	224 (72.0%)	4 (2.2%)
>5 Weeks	193 (32.9%)	737 (60.1%)	1268 (81.2%)	199(39.25%)	2204 (66.8%)	394 (72.2%)	214 (68.8%)	0
>6 Weeks	35 (6.0%)	662 (54.0%)	1115 (71.4%)	179 (35.2%)	1956 (59.3%)	345 (63.2%)	96 (30.9%)	0
>3 Months	0	513 (41.8%)	893 (57.2%)	121 (23.8%)	1527 (46.3%)	284 (52.0%)	46 (14.8%)	0
>6 Months	0	404 (32.9%)	742 (47.5%)	64 (12.6%)	1210 (36.7%)	236 (43.2%)	36 (11.6%)	0
>12 Months	0	237 (19.3%)	441 (28.2%)	22 (4.3%)	700 (21.2%)	24 (4.4%)	6 (1.9%)	0

Data Source: ISS Table 31.1.1 and ISS Table 32.1.1.

Table includes data from all phases of Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101 and period 1 of Study 2328.

Duration of treatment was based on the patient's total exposure to any individual study drug. If a patient was exposed to multiple study drugs in a clinical study, then the patient has been represented in the safety analyses once for each drug. For example, if a patient was assigned initially to placebo in the short-term phase and reassigned to iloperidone in the long-term phase and/or the open-label extension, then this patient has been counted twice (once for each of the 2 study drugs) in the safety tabulations.

Based on the sponsor's table, a total of 1210 patients (37% of all 3297 patients) had an exposure to iloperidone of over 6 months. Only 64 of these 1210 patients were assigned to a 20-24 mg/day dose group. A total of 700 patients (21% of all 3297 patients) had an exposure to iloperidone over 1 year. Only 22 of these 700 patients were assigned to a 20-24 mg/day dose group. Five hundred and eight patients (26%) of all 3297 patients were assigned to a 20-24 mg/day dose group.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Due to study design, Studies ILPB202, ILPB103, ILO5220105, ILO5220104, VP-VYV-683-1001, VP-VYV-683-1002, ILPB106, ILO5220110, ILPB101/101A, ILPB102, ILPB105, ILO5222301, ILPB203, ILO5220112, ILPB200, ILPB201, ILO522B210, ILO5220102, ILO5220103, ILO5220107, ILO5220108, ILO522A0109, ILP2001ST, ILP2001LT, ILP3007P1, ILP3007P2, ILP3001, ILP3002, ILP3003, ILO5222328, ILPB104, ILPB199, ILPB205, and ILPB303) and the extension phases of Studies 3000, 3004, and 3005 (ILP3000LT, ILP3004 LT, and ILP3005 OLE) were not included in the primary safety database.

7.2.2.2 Literature

According to the sponsor's 9/27/07 submission, review of the literature is not applicable as there are no publications from studies other than those included in the clinical development program of iloperidone. However, in their Response to Issues Described in the Filing Communication contained in their 1/4/08 email, they refer to Section 5.3 of the 120-Day Safety Update. This will be reviewed by Phillip Kronstein, M.D., Clinical Reviewer.

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience is not adequate. ICH guidelines specify that the number of patients treated for 6 months at dosage levels intended for clinical use should be adequate to characterize the pattern of adverse drug events over time (usually 300-600 patients) and that 100 patients exposed for a minimum of one year at dosage levels intended for clinical use is considered acceptable. The possibly effective dosage level for iloperidone is 24 mg/d, and only 64 patients who were assigned to a 20-24 mg/d dose group had a duration of exposure for over 6 months. Only 22 patients who were assigned to a 20-24 mg/d dose group had a duration of exposure for over 12 months. The number of patients actually receiving a mean daily dose of 24 mg/d is very likely less.

7.2.4 Adequacy of Routine Clinical Testing

Without more detailed information, it is not clear whether routine clinical testing was adequate.

7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

A Clinical Pharmacology and Biopharmaceutics review was not available at the time of completion of this review. Per 5/14/08 emails from Andre Jackson, Ph.D., OCPB Reviewer, issues of concern included the genomic data analysis. The sponsor did not classify the extensive and poor metabolizers appropriately, and it was difficult to make meaningful comparisons between these two groups. Also, the hepatic study was confounded and needs to be repeated.

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

There are no recommendations for further study.

7.2.7 Assessment of Quality and Completeness of Data

An audit of the Case Report Forms (CRF's), Narrative Summaries, and adverse event data listings for the double-blind phase of Studies 3000, 3004, 3005, and 3101 was performed. Approximately[31] 420 CRF's were submitted, and the undersigned reviewer randomly selected 8 patients[32] (2% of these CRF's) and examined the CRF's, Narrative Summaries, and adverse event data listings.

An examination of the adverse event information across these sources for these 8 patients revealed multiple inconsistencies and lack of completeness. Note that this evidence of inconsistencies and lack of completeness is in addition to the examples of inconsistencies and lack of completeness noted in Sections 7.1.1, 7.1.2, and 7.1.5.2.

For Patient #510/1027 from Study 3000, the CRF and Narrative Summary were reasonably consistent and complete. However, the adverse event data listing was missing for this patient.

For Patient #532/1006 from Study 3000, the study completion CRF reported that the patient was discontinued from the study due to unsatisfactory therapeutic effect on 1/21/99. However, the "Action taken" column of the Adverse events CRF reported that elevated CPK values started on 1/20/99 and led to "study drug permanently discontinued due to this adverse event" and "hospitalization/prolonged hospitalization".

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[31] Because the sponsor did not provide an enumeration of the Case Report Forms (CRF's), the exact number of submitted CRF's is unknown.
[32] These consisted of 2 patients from Study 3000 (510/1027, 532/1006), 2 patients from Study 3004 (173/1002, 621/1001), 2 patients from Study 3005 (510/1015, 612/1007), and 2 patients from Study 3101 (017/0011, 003/0033).

For Patient #621/1001 from Study 3004, the adverse event data listing of "exacerbation of schizoaffective" was not noted on the CRF. Also of note, the adverse event of headache noted in the CRF was not described in the Narrative Summary.

For Patient #510/1015 from Study 3005, the adverse event data listing and Narrative Summary showed an adverse event of suicidality, which was not noted in the adverse event CRF. Also of note, the adverse event of headache was crossed out on the adverse events CRF on 3/9/01, while the adverse event was recorded on 12/14/00.

For Patient #612/1007 from Study 3005, the Narrative Summary cites unsatisfactory therapeutic effect as reason for premature study discontinuation. However, the CRF notes that the primary reason for premature discontinuation was adverse event. Also of note, the adverse event of migraine headache noted in both the CRF and adverse event data listing was not noted in the Narrative Summary.

For Patient #017/0011 from Study 3101, the CRF and adverse event data listing were consistent. However, none of the noted adverse events were contained in the Narrative Summary.

For Patient #003/0033 from Study 3101, the CRF and adverse event data listing were consistent. However, only one of the 18 adverse events noted was included in the Narrative Summary.

7.2.8 Additional Submissions, Including Safety Update

The clinical safety cut-off date for the NDA was 12/4/06. The open label extension phase of study 3101 was still ongoing at that time, but the database was subsequently locked on 3/21/07. No clinical studies are ongoing at this time. The data cut-off date was May 4, 2007 for the 4-Month Safety Update. The clinical data contained in the 4-Month Safety Update will be reviewed by Phillip Kronstein, M.D., Clinical Reviewer.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Overall clinical experience is not adequate, with less than 64 patients and less than 22 patients having a duration of exposure for over 6 months and over 12 months, respectively, at the possibly effective dosage level of 24 mg/d. Thus, there is insufficient information to determine whether iloperidone is safe for use at this dose level.

Moreover, the integrity of the sponsor's existing safety data is questionable, given that an audit of patient CRFs, Narrative Summaries, and adverse event data listings revealed deficiencies in 7 out of the 8 examined, in addition to multiple deficiencies and discrepancies in the safety database which were incidentally noted.

Safety findings in the deaths, serious adverse events, and adverse events leading to dropout database include sudden deaths, seizures, arrhythmias, hypotension, syncope, priapism, and elevated creatine phosphokinase (CPK).

Safety findings in the controlled database include QTc prolongation, orthostatic hypotension, weight gain, anemia, high prolactin, and tachycardia.

A summary of the review of the safety data follows:

- Ten deaths were considered possibly related to iloperidone treatment, and had three apparent general causes: suicide-related (4 deaths), cardiac-related (5 deaths), and diabetes mellitus-related (1 death). All of the cardiac-related deaths were sudden in nature. This finding, in light of multiple cases of arrhythmias, hypotension, and syncope is concerning.
- Twenty two SAE's were considered medically serious and possibly related to iloperidone treatment, and can be grouped into 9 general categories: seizures (8 SAE's), arrhythmias (3 SAE's), hypotension (3 SAE's), syncope (2 SAE's), priapism (2 SAE's), increased CPK (1 SAE), MI (1 SAE), tachycardia (1 SAE), and dizziness (1 SAE).
- Ten adverse events leading to dropout were considered possibly related to iloperidone treatment, and can be grouped into 6 general categories: syncope (3 events), increased CK (2 events), increased liver enzymes (2 events), arrhythmia (1 event), cardiac-related (1 event), and priapism (1 event).
- There were 4 events of marked hypotension, including one resulting in death, in the deaths, serious adverse events, and adverse events leading to dropout uncontrolled database, without any findings in the mean change from baseline or PCI analyses.
- There were 5 events of elevated CPK (ranging from 398 to 21,750 U/L) in the deaths, serious adverse events, and adverse events leading to dropout database without any findings in the mean change from baseline or PCI analyses or any reported seizure activity.
- The sponsor did not perform appropriate adverse event incidence analyses using the controlled database for the adverse events of seizures, arrhythmias, syncope, or priapism.
- Two adverse events that led to dropout occurred in at least 1% of iloperidone-treated patients and at a rate higher than that for placebo patients: dizziness (10-16 mg/d) and orthostatic hypotension (10-16 mg/d).
- Based on PCI analyses, it appears iloperidone may cause anemia and high prolactin. Based on mean change from baseline analyses, it appears that iloperidone may cause orthostatic hypotension. Based on mean change from baseline analyses and PCI analyses, it appears that iloperidone may cause weight gain (dose-related mean change of 1.5 to 2.7 kg). Based on PCI analyses, it appears that iloperidone may cause tachycardia and systolic hypotension. Based on mean change from baseline analyses and PCI analyses, iloperidone prolongs QTcF (dose-related mean change of 2.5 to 8.7 msec). A cursory review of the thorough QT study and preclinical data confirms iloperidone's prolongation of the QTc interval.

Important limitations of the data include inappropriate splitting and coding of adverse events; use of $p<0.05$ instead of 0.10 for mean change from baseline analyses for labs, VS, and ECG's; absence of data for dropouts due to labs, VS and ECG's analyses; absence of PCI analysis for

abnormal ECG rhythm; absence of information to determine whether routine clinical testing (for urinalysis, vital signs, and ECG's) was adequate; and absence of the range of outlier values included in the outlier analyses.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The double-blind phase of four of the placebo-controlled studies (Studies 3000, 3004, 3005, and 3101) were pooled to estimate the incidence of adverse events. The sponsor did not pool the fifth placebo-controlled study (Study B202).

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Please see Section 7.1.5.6

7.4.2.2 Explorations for drug-demographic interactions

Please see Section 7.1.5.6.

7.4.2.3 Explorations for drug-disease interactions

There were no studies addressing drug-disease interactions in this submission.

7.4.2.4 Explorations for drug-drug interactions

There were no studies addressing drug-drug interactions in this submission.

7.4.3 Causality Determination

Adverse events were considered common and possibly drug-related if they were reported in at least 5% of the iloperidone patients at a rate at least twice that in the placebo group in the double-blind phase of Studies 3000, 3004, 3005, and 3101.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Study 3101 was a fixed dose study of iloperidone that examined a dose of 12 mg bid versus placebo in the treatment of schizophrenia. This dose group produced a significant difference over placebo. Dosing for iloperidone began at 1 mg bid at Day 1 and was increased to 2 mg bid at Day 2, 4 mg bid at Day 3, 6 mg bid at Day 4, 8 mg bid at Day 5, 10 mg bid at Day 6, and 12 mg bid at Day 7.

Study 3005 was a flexible dose study of iloperidone that examined doses of 6-8 mg bid and 10-12 mg bid versus placebo in the treatment of schizophrenia. Patients were randomized to 6-8 mg bid and 10-12 mg bid treatment groups. For both dose groups, dosing for iloperidone began at 1 mg bid for the first day of treatment and was increased to 2 mg bid at Day 2, 4 mg bid at Day 3, and 6 mg bid at Day 4. For the 10-12 mg bid dose group, dosage was increased to 8 mg bid at Day 5 and 10 mg bid at Day 6. From Day 8 to 42, dosage was flexible (6 to 8 mg bid for the 6-8 mg bid group, and 10 to 12 mg bid for the 10-12 mg bid group).

Since Study 3101 was a single dose study and Study 3005 was a flexible dose study, no conclusions can be made regarding dose response for efficacy.

8.2 Drug-Drug Interactions

One death involved 3 days of concomitant treatment with an antihistamine, chlorpheniramine, and triprolidine/pseudoephedrine just prior to death. There were no other serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

8.3 Special Populations

Please see Section 6.1.4.

8.4 Pediatrics

At the 9/7/05 End of Phase 2 meeting, the Division indicated their agreement with a waiver for iloperidone for patients below the age of 13 and a deferral for the assessment of the effects of iloperidone in patients between the ages 13 and 18 until assessments in adults have been completed.

8.5 Advisory Committee Meeting

This submission was not presented to the Psychopharmacologic Drugs Advisory Committee.

8.6 Literature Review

See Section 7.2.2.2.

8.7 Postmarketing Risk Management Plan

Since the undersigned reviewer is recommending a Not Approvable action, a postmarketing risk management plan is not applicable.

8.8 Other Relevant Materials

The Division of Drug Marketing, Advertising, and Communications (DDMAC) found the sponsor's initially proposed proprietary name, Fiapta, acceptable from a promotional perspective (OSE review #2007-537, dated 4/14/08).

The Division of Medication Error Prevention (DMETS) does not recommend the use of the proprietary name Fiapta because it possesses strong orthographic similarities to Lipitor. They will proceed with an assessment of the alternate name, Fanapta, which will be forwarded in a separate review, and was not available at the time of completion of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

There are 3 negative studies, 2 positive studies, and 3 studies in which an active comparator was found to be superior to iloperidone. Only one study showed an effect size of iloperidone comparable to the active comparator, with an OC analysis corroborating the MMRM analysis at most time points for the active comparator, but not iloperidone. Thus, the sponsor has not provided substantial evidence that supports the claim of short-term efficacy for the use of iloperidone in schizophrenia.

Of note, data from at least one of the Study 3101 sites was not considered to be reliable in support of this NDA and 47% of the ITT patients in Study 3005 were contributed by sites where information on investigator financial interests were unobtainable.

Overall clinical experience is not adequate, with less than 64 patients and less than 22 patients having a duration of exposure for over 6 months and over 12 months, respectively, at the

possibly effective dosage level of 24 mg/d. Thus, there is insufficient information to determine whether iloperidone is safe for use at this dose level.

Moreover, the integrity of the sponsor's existing safety data is questionable, given that an audit of patient CRFs, Narrative Summaries, and adverse event data listings revealed deficiencies in 7 out of the 8 examined, in addition to multiple deficiencies and discrepancies in the safety database which were incidentally noted.

Safety findings in the deaths, serious adverse events, and adverse events leading to dropout database include sudden deaths, seizures, arrhythmias, hypotension, syncope, priapism, and elevated creatine phosphokinase (CPK).

Safety findings in the controlled database include QTc prolongation, orthostatic hypotension, weight gain, anemia, high prolactin, and tachycardia.

9.2 Recommendation on Regulatory Action

In accordance with 21 CFR 312.120, it is recommended that this application be granted Not Approvable status on the basis of insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling [314.125 (b)(4)] and lack of substantial evidence consisting of adequate and well-controlled investigations that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling[314.125 (b)(5)].

9.3 Recommendation on Postmarketing Actions

Since the undersigned reviewer is recommending a Not Approvable action, postmarketing actions are not applicable.

9.3.1 Risk Management Activity

Since the undersigned reviewer is recommending a Not Approvable action, risk management activity is not applicable.

9.3.2 Required Phase 4 Commitments

Since the undersigned reviewer is recommending a Not Approvable action, required phase 4 commitments are not applicable.

9.3.3 Other Phase 4 Requests

Since the undersigned reviewer is recommending a Not Approvable action, other phase 4 requests are not applicable.

9.4 Labeling Review

Since the undersigned reviewer is recommending a Not Approvable action, a labeling review was not performed.

9.5 Comments to Applicant

Should an action other than Not Approvable be taken, it is recommended that the following be conveyed to the sponsor:

1. Please provide all hospital records, a table with all laboratory results by date, and any additional records and lab results, including any culture results, CK-MB fraction results, HIV test results, ECG's, and vital signs, for Subject #ILP3002 092-1010.
2. Please provide all hospital records, all ECG's, and any additional records and lab results, including arterial blood gas and CK-MB fraction results, for Subject #ILP3003-502-1037.
3. For Patient #'s CILO522A2328-0522-00006, ILP2001-502-1005, ILP3003-626-1009, ILP3001-054-1001, ILP3001-098-1011, ILP3003-626-1009 please provide all ECG's.
4. For Patient #VP-VYV-683-3101 003-0033, please provide all bilirubin levels.
5. Please describe when urinalysis data was obtained (i.e., at what time points) for Study Group 2.
6. Please describe vital signs testing procedures (i.e., which vital signs were obtained at which time points) for Study Group 2.
7. Please describe when ECG testing was performed (i.e., at what time points) for Study Group 2.
8. Please provide a listing of all adverse events in all iloperidone clinical studies.
9. Please provide a line listing and incidence all dropouts due to laboratory abnormalities for Study Group 2, by dose group.
10. Please provide a line listing of all dropouts due to vital sign abnormalities, including weight, for Study Group 2, by dose group.
11. Please provide a line listing of all dropouts due to ECG abnormalities for Study Group 2, by dose group.
12. Please provide an ANCOVA analysis comparing iloperidone dose groups vs. placebo on mean change from baseline to endpoint, controlling for baseline, for all serum laboratory test results using a p-value < 0.10, for the Study Group 2 Safety Population.
13. Please provide an ANCOVA analysis comparing iloperidone dose groups vs. placebo on mean change from baseline to endpoint, controlling for baseline, for

all vital signs values using a p-value < 0.10, for the Study Group 2 Safety Population.

14. Please provide a statistical analysis (e.g., ANCOVA analysis using a p-value <0.10) on the mean change from baseline data for ECG parameters of heart rate, PR interval, QRS interval, and RR interval for the Study Group 2 Safety Population.
15. Please provide an outlier analysis for ECG rhythm changes from sinus rhythm to any other rhythm.
16. In section 5.5 of your Summary of Clinical Safety, you report overdoses "including only the short-term phase of Study 3101". Please report all overdoses in all iloperidone clinical studies.
17. Please provide a table summarizing overall exposure to iloperidone by therapy according to mean daily dose and duration of therapy. This should follow the format of ISS Table 10 but describe mean daily dose instead of treatment group assignment, and include all iloperidone studies.
18. Please provide information on withdrawal of your product in other countries and submission of marketing authorization applications to foreign regulatory agencies.
19. Please provide information regarding the ethical conduct of Study B202.
20. In the second paragraph of your Introduction to the CTD, it appears you are stating that there are a total of 32 studies. However, based on the data in your submission, it appears there are 38 studies. Please clarify.
21. For Study 3101ST, please provide a primary efficacy analysis, removing all patients receiving concomitant antipsychotic medication (e.g., quetiapine, olanzapine, ziprasidone, fluphenazine, thorazine, haloperidol, risperidone, aripiprazole). Also, please provide a line listing for the removed patients.
22. For Study 3005ST, please provide the percentages of ITT population patients (excluding patients diagnosed with schizoaffective disorder) using concomitant medications and the most frequently used concomitant medications.
23. For Study 3005ST, please provide an enumeration of patients (excluding patients diagnosed with schizoaffective disorder), by treatment group, identified as protocol violators because of prohibited medication use.
24. For Study 3005ST, please provide an OC analysis (excluding patients diagnosed with schizoaffective disorder) for the primary efficacy variable by treatment week.
25. For Study 3101ST, please provide a table similar to Table 8 on page 54 of 1489 in your CSR for Study 3101ST, showing patient disposition by treatment group, but utilizing the MITT population.
26. For Study 3101ST, please provide the percentages of MITT population patients using concomitant medications during the double-blind phase of the study and the most frequently used concomitant medications.
27. For Study 3101ST, please provide an enumeration of patients (excluding patients diagnosed with schizoaffective disorder), by treatment group, identified as protocol violators because of prohibited medication use.

28. We note Item 3 in your Response to 9May08 Information Request contained in your 14 May 08 email. If this adverse events thesaurus was not used for all the studies in the Study Group 2 safety population, please provide any verbatim terms from the Study Group 2 safety population with their associated preferred terms not included in your 14 May 08 response. Alternatively, please state that the adverse events thesaurus submitted 14 May 08 was used for all the studies in the Study Group 2 safety population, if this was the case.
29. Inspection of your adverse events thesaurus revealed that the following verbatim terms were inappropriately coded to preferred terms. Please recode them to convulsion, convulsion, extrayramidal disorder, hypotension, hypotension, tachycardia, and arrhythmia respectively, and update any affected sections of labeling accordingly.
    a. generalized tonic clonic convulsion
    b. generalized tonic clonic seizure
    c. parkinsonism (pains in back)
    d. hypotension (arterial)
    e. arterial hypotension
    f. hypotension with symptom of supine bp 118/54
    g. tachycardia (post-operative complication-AE per investigator decision)
    h. paroxysmal atrial tachycardia-palpitations
30. Please combine the following MedDRA terms (after recoding as requested above), and update any affected sections of labeling accordingly:
    a. convulsion, tonic clonic movements, grand mal convulsion
    b. tachycardia, tachyarrhythmia, sinus tachycardia, heart rate increased
    c. bradycardia, sinus bradycardia
    d. syncope, syncope vasovagal, loss of consciousness
    e. abdominal discomfort, stomach discomfort, dyspepsia
    f. sedation, hypersomnia, somnolence
    g. proteinuria, protein in urine present
    h. extrapyramidal disorder, parkinsonism, parkinsonian rest tremor, tremor (with EPS, extrapyramidal, parkinson, and parkinsonism mentioned in the verbatim term), parkinsonian gait, movement disorder (with EPS, extrapyramidal, or parkinsonism mentioned in the verbatim term), masked facies, difficulty in walking (with parkinsonism mentioned in the verbatim term), cogwheel rigidity, back pain (with parkinsonism mentioned in the verbatim term)
    i. pyrexia, body temperature increased
    j. hypertension, blood pressure increased
    k. orthostatic hypotension, postural orthostatic tachycardia syndrome, blood pressure orthostatic
    l. hypotension, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased
    m. rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular

n. pruritis, pruritis generalized

31. Please provide common adverse events data (i.e., >2% table following the format of Table 21 on page 46 of 256 of Section 2.7.4) by dose group for the Study Group 2 safety population, after recoding and combining preferred terms as requested above.
32. Please perform subgroup analyses of demographic variables (age, gender, and race) on the reporting rates of the common and drug-related adverse events (i.e., reported in at least 5% of any iloperidone dose group at a rate at least twice that in the placebo group), after recoding and combining preferred terms as requested above.
33. For the Study Group 2 Safety Population, please provide the incidences and risk ratios, with 95% confidence intervals, for the following preferred terms (or combinations of preferred terms) by dose group, after recoding and combining preferred terms as requested above.
    a. Arrhythmia, cardiac flutter, heart rate irregular, first degree AV block, ventricular extrasystoles, extrasystoles
    b. Convulsion
    c. Syncope
    d. Suicidal ideation, suicidal attempt
    e. Priapism, painful erection
34. Please provide the range of outlier values included in your outlier analyses for low Hgb, low Hct, low RBC, high prolactin, pulse rate $\geq$ 120 bpm, pulse rate increase $\geq$ 15 bpm, SBP $\leq$ 90 mm Hg, weight increase $\geq$ 7% contained in your "Responses to Filing Communication" for the Study Group 2 safety population in your 1/10/08 email.

Michelle M. Chuen, M.D.
June 13, 2008

cc: NDA 22-192
HFD-130/Division File
HFD-130/MChuen
/PKronstein
/RLevin
/NKhin
/MMathis
/TLaughren
/KUpdegraff

10 APPENDICES

10.1 Review of Individual Study Reports

Study 3000

Investigators/Sites
Fifty one investigators conducted this study at 45 sites in the U.S. Investigators and sites are listed in Appendix 10.3.1 in Section 10.3 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial was to determine the efficacy and safety of iloperidone 4, 8 and 12 mg/d (administered as 2, 4 and 6 mg b.i.d.) and haloperidol 15 mg/d (7.5 mg b.i.d.) compared with that of placebo over 42 days in schizoaffective or schizophrenic patients with acute or subacute exacerbation.

Patient Sample
Important inclusion criteria were:

- age 18 to 65 years, inclusive. Patients older than 65 years were considered on a case-by-case basis.
- male, surgically sterilized female, postmenopausal female, or non-pregnant female of childbearing potential who agreed not to attempt to get pregnant and to use contraception
- diagnosed with schizophrenia according to DSM-IV criteria. This included DSM-IV diagnosis of schizophrenia (i.e., 295) with suffixes 10 (disorganized), 20 (catatonic), 30 (paranoid), 60 (residual), 70 (schizoaffective), or 90 (undifferentiated).
- met criterion A symptoms of the DSM-IV schizophrenia criteria for at least the 2 weeks prior to baseline
- had PANSS Total (PANSS-T) score of at least 60
- had a rating of at least "4" ("moderate") on at least 3 of the following 5 symptoms on the PANSS Positive Syndrome: delusions, conceptual disorganization, hallucinatory behavior, grandiosity and suspiciousness/persecution
- were in need of treatment with an antipsychotic medication
- had vital signs measurements within normal ranges, defined for healthy adults as supine blood pressure in the range of 100-160 mm Hg systolic and 60-95 mm Hg diastolic, with a supine radial pulse of 60-100 beats per minute (bpm)
- were medically acceptable for oral treatment with iloperidone or haloperidol, as confirmed by medical history, physical examination, electrocardiogram (ECG), and clinical laboratory tests, which were within the normal range, or, if abnormal, judged not to be clinically significant.

The following were relevant exclusion criteria:

- met the DSM-IV criteria for schizophreniform disorder (295.40) or met any other primary psychiatric diagnosis (Axis I) according to DSM-IV criteria
- had diagnosis or history suggestive of chemical dependence, according to DSM-IV criteria, or toxic psychosis in the preceding 6 months, or a clinical presentation possibly confounded by the use of recreational drugs or alcohol
- were mentally retarded (moderate to severe), in a comatose state, or with significant brain trauma
- had a history of suicide attempt within the last year, or, in the opinion of the Investigator, were currently at imminent risk of suicide
- suffered from significant physical illness in the 4-week period preceding baseline
- had other medical conditions that could be expected to progress, recur, or change to such an extent that they may put the patient at special risk or bias the assessment of the clinical and the mental status of the patient to a significant degree
- had a current diagnosis or recent past history of epilepsy, major head trauma, or progressive neurological disease (other than tardive dyskinesia or drug-induced extrapyramidal side-effects)
- had past history of priapism treated with surgical intervention.
- was known to have hypersensitivity to drugs chemically related to benzisoxazoles or butyrophenones
- received during the 30 days preceding baseline any drug known to cause major organ system toxicity (e.g., chloramphenicol or tamoxifen)
- received electroconvulsive therapy (ECT) in the 3 months prior to baseline
- was likely to require continuous treatment with any other psychotropic drug (other than short-acting benzodiazepines), including antidepressants or mood stabilizers, during the entire study duration
- needed treatment with anticholinergic drugs during the 24 h prior to baseline evaluations (i.e., baseline day and the day before baseline) Note: Use of an anticholinergic drug on a p.r.n. basis for the treatment of extrapyramidal symptoms emerging at any other time during the study was permitted
- experienced neuroleptic malignant syndrome (rigidity/rigor, hyperpyrexia, and creatinine phosphokinase [CPK] concentrations greater than two times the upper normal limit)
- received clozapine within 60 days prior to screening
- suffered from psychotic symptoms that failed to improve (based upon the Investigator's opinion) following sufficient exposure to a therapeutic dose of any antipsychotic treatment over the last 2 years
- was previously randomized to treatment in this study or in other studies with iloperidone since 1997

Design

This was a prospective, randomized, double-blind, parallel-group, multicenter study with three phases: pre-randomization, initial placebo- and haloperidol-controlled double-blind (6-week) and long-term (98-week). This was followed by an open-label extension. The pre-randomization

phase consisted of a screening period and a placebo run-in period. The screening visit occurred between 3 and 30 days prior to baseline (Day 0). The single-blind placebo run-in period lasted 3 days (i.e., Days -2, -1 and 0), during which all patients were administered placebo capsules.

The 6-week initial double-blind phase consisted of titration and maintenance periods. Twice daily (b.i.d.) dosing was followed throughout this phase. In the titration period (Days 1-7), fixed-dosing regimens were used. Although patients in different treatment groups reached their target doses on different days, the titration period for all treatment groups covered the first 7 days for study design purposes. In the maintenance period (Days 8-42), treatment was continued at the fixed target dose for 5 weeks. Patients not tolerating or benefiting from their initial double-blind treatment after completing 28 days were permitted to enter directly into the long-term phase.

After completing the 6-week initial double-blind phase, patients had the option to continue treatment in the long-term phase of the study, during which patients who received iloperidone were restarted at a dose of 4 mg/d iloperidone, patients who received haloperidol were restarted at a dose of 5 mg/d haloperidol, and patients who received placebo were treated with iloperidone: 1 mg/d on Day 43, 2 mg/d on Day 44, and 4 mg/d on Day 45. Beginning on Day 50, flexible doses of iloperidone 4-16 mg/d and haloperidol 5-20 mg/d were utilized.

The long-term and open-label extension phases will not be discussed further in this section, due to lack of a placebo control.

The dosing schedule for the pre-randomization and initial double-blind phases are summarized in the table below, extracted from the sponsor's submission.

Pre-randomization phase		Initial double-blind phase (b.i.d. dosing)	
Screening	Single-blind placebo run-in	Titration period (fixed dose increases every other day until the target dose was reached)	Maintenance period (fixed doses)
Days -30 to -3	Days -2 to 0 [a]	Days 1 to 7	Days 8 to 42
Screening visit	Pbo (b.i.d. dosing)	Ilo: 2→4 mg/d	Ilo: 4 mg/d
		Ilo: 2→4→8 mg/d	Ilo: 8 mg/d
		Ilo: 2→4→8→12 mg/d	Ilo: 12 mg/d
		Hal: 2→5→10→15 mg/d	Hal: 15 mg/d
		Pbo	Pbo

Ilo=iloperidone; Hal=haloperidol; Pbo=Placebo

Patients were instructed to take the study medication in the morning and evening, at approximately 8 a.m. and 6 p.m., respectively. Study medication could be taken with or without food.

If patients were discontinued prematurely, the Day 42 (final visit) assessments were performed at end of treatment. Unsolicited AE reports occurring up to 30 days after last dose of investigational product were recorded together with concomitant medications in appropriate sections of the pCRF.

The PANSS was administered at screening, baseline, Day 7, Day 14, Day 21, Day 28, Day 35, and Day 42 or at study completion. For the weekly visits, a window of up to 3 days was allowed for flexibility in scheduling the visits.

Efficacy Assessments
The protocol-defined primary efficacy variable was the Positive and Negative Syndrome Scale (PANSS) total score. No key secondary variables were identified.

Efficacy Analysis
The intent-to-treat (ITT) patients were those who:

- were randomized
- received at least one dose of double-blind study medication
- from whom at least one efficacy measurement was obtained while on study medication

The primary outcome measure was the change from baseline to endpoint or early termination in the Positive and Negative Syndrome Scale (PANSS) total score. This measure was analyzed using an analysis of covariance (ANCOVA) model based on the LOCF data set of the initial double-blind phase. The primary treatment comparison was the mean of the iloperidone 8 mg and 12 mg groups versus placebo in the primary efficacy analysis. Iloperidone was considered efficacious if the average of the mean responses of the two dose groups was significantly superior to placebo in this comparison. A two-way analysis of covariance (ANCOVA) model was used for the analysis of treatment main effect of continuous variables. The terms in the model included treatment, center, baseline (as covariate), and the treatment-by-baseline term. An additional analysis was performed for the exploration of treatment-by-center interaction by adding this interaction term to the above ANCOVA model. If a treatment-by-center interaction was detected, the interaction was explored in an ad-hoc manner.

Baseline Demographics
The table below displays the demographic characteristics of the randomized patient sample (including schizoaffective patients)[33] by treatment group. No patient under age 18 or over age 68 participated in this study. There were no major differences among the 5 treatment groups with respect to age, gender, or race.

[33] This information was not provided for the ITT population.

TABLE 10.1.1 : STUDY 3000[34] BASELINE DEMOGRAPHICS, RANDOMIZED POPULATION[35]								
Treatment (n)	**Age (yrs)**		**Sex (%)**		**Race (%)**			
	Mean	**Range**	**Male**	**Female**	**White**	**Black**	**Oriental**	**Other**
Iloperidone 4 mg/d (121)	38.4	21-65	68	32	47	43	2	8
Iloperidone 8 mg/d (125)	37.0	18-68	75	25	39	46	1	14
Iloperidone 12 mg/d (124)	40.1	18-68	73	27	54	35	2	9
Haloperidol 15 mg/d (124)	39.1	19-59	69	31	47	44	2	7
Placebo (127)	39.3	19-66	71	29	50	43	0	6

Baseline Severity of Illness
For the randomized patients (including schizoaffective patients), treatment groups had no major differences with respect to mean baseline PANSS total score[36] (mean scores of 95.2 in Ilo 4 mg/d patients, 96.0 in Ilo 8 mg/d patients, 95.8 in Ilo 12 mg/d patients, 95.7 in Hal 15 mg/d patients, and 94.6 in placebo patients).

Patient Disposition
Six hundred twenty one (621) patients (including schizoaffective patients) were randomized in this study. Of these patients, 613 received at least one dose of double-blind study medication. Six hundred ten (610) patients received at least one dose of double-blind study medication and had at least one subsequent safety evaluation during Days 1-42 and comprised the safety population. Five hundred seventy three (573) patients comprised the ITT sample (113 Ilo 4 mg/d patients, 114 Ilo 8 mg/d patients, 115 Ilo 12 mg/d patients, 114 Hal 15 mg/d patients, and 117 placebo patients).

The numbers of ITT patients in-study over time (including schizoaffective patients) are displayed in Appendix 10.3.3 in Section 10.3. At Day 42, 46% (52/113) of Ilo 4 mg/d patients, 39% (45/114) of Ilo 8 mg/d patients, 45% (52/115) of Ilo 12 mg/d patients, 38% (43/114) of Hal 15 mg/d patients and 34% (40/117) of placebo patients completed the study. Based on the

[34] Figures may not add up to 100% due to rounding.
[35] This information was not provided for the ITT population.
[36] This information was not provided for the ITT population.

randomized population (including schizoaffective patients),[37] overall dropout rates were high, but there were no major differences among treatment groups [57% (69/121) of Ilo 4 mg/d patients, 64% (80/125) of Ilo 8 mg/d patients, 58% (72/124) of Ilo 12 mg/d patients, 65% (81/124) of Hal 15 mg/d patients, and 69% (87/127) of placebo patients]. Based on the randomized population (including schizoaffective, there were also no major differences among dropout rates due to unsatisfactory therapeutic effect [30% (36/121) of Ilo 4 mg/d patients, 30% (38/125) of Ilo 8 mg/d patients, 29% (36/124) of Ilo 12 mg/d patients, 25% (31/124) of Hal 15 mg/d patients, and 35% (44/127) of placebo patients].

Dosing Information
This was a fixed dose study.

Concomitant Medications
All comorbid illnesses were treated in accordance with prevailing medical practice.

Medications with known central nervous system effects (e.g., antidepressants, anxiolytics, mood stabilizers, sedative/hypnotics, or psychostimulants), which were likely to interfere with study assessments, were prohibited during the study. Patients were to be weaned from these medications prior to hospital admission for the placebo run-in period, so that at baseline they would be receiving no psychotropic medications, except as indicated below.

Antipsychotic treatment taken prior to study enrollment were to be discontinued according to the following criteria:
• patients who had not recently received treatment with a neuroleptic were to have a minimum placebo run-in period of 3 days
• patients who had recently received treatment with an oral neuroleptic were to have a minimum placebo run-in period of 3 days, or longer, if appropriate
• patients who had recently received treatment with a depot neuroleptic were to receive no injections for at least one treatment cycle without use of other neuroleptics prior to the beginning of the 3-day placebo run-in period

One exception to the requirement for discontinuation of psychoactive medications was for patients who were taking low doses of short-acting benzodiazepines (e.g., alprazolam) and had been at a stable dose for 1 month prior to baseline. These patients were to be allowed entry into the study and were to continue with their treatment at the same dose and dose regimen. Patients who required a significant dose increase in their benzodiazepine therapy were to be discontinued from further study participation.

Additionally, patients receiving chloral hydrate for insomnia, agitation, or severe restlessness prior to baseline were to be allowed to enter the study.

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[37] This information was not provided for the safety population.

Only the following concomitant medications were to be allowed for the treatment of insomnia:
• Chloral hydrate (prn, 500 mg p.o., up to 2000 mg/d total); or
• Zolpidem (prn, 5-10 mg/d p.o.).

Additionally, if these medications were administered, at least 8 h were to elapse prior to completing any efficacy evaluation.

Only the following concomitant medications were to be allowed for the treatment of agitation or severe restlessness:
• Chloral hydrate (prn, 500 mg p.o., up to 2000 mg/d total);
• Sodium amytal (prn, 30-50 mg/im injection, up to 3 injections/d over up to 6 consecutive days); or
• Lorazepam (prn, up to 3 mg/im injection, up to 6 mg/d total; may be administered during the placebo run-in period and during the first 14 days of the initial double-blind phase)

For the duration of the study, lorazepam (as above) could be administered up to three times during any 6-week period. Additionally, if chloral hydrate, sodium amytal, or lorazepam were administered, at least 4 h were to elapse prior to completing any efficacy evaluation.

Anticholinergic drugs for the treatment of extrapyramidal symptoms (EPS) were to be allowed during the placebo run-in period. However, EPS must have improved and anticholinergic medication discontinued for at least 24 h prior to baseline (baseline day and the day prior to baseline). Use of an anticholinergic drug on a prn basis for the treatment of extrapyramidal symptoms emerging during the active-treatment phase of the study was permitted.

Only benztropine mesylate treatment could be initiated for extrapyramidal symptoms after randomization to active treatment and only after an assessment of EPS by ESRS examination is completed. In case of severe EPS (e.g., acute dystonic reaction), the Investigator could treat the dystonia with a parenteral intramuscular injection of benztropine mesylate for immediate relief of symptoms, then complete an ESRS during the period when the effect of the medication is diminished, but prior to initiating treatment with oral benztropine mesylate, if necessary.

No other medications for treatment of EPS were allowed. Any treatment-emergent AE (e.g., insomnia, agitation, or EPS) severe enough to require the initiation of pharmacologic treatment was to be recorded on the AE page of the CRF.

Beta-blockers could not be initiated during the study for any indication. Diphenhydramine hydrochloride was excluded from use in the study for a psychiatric indication or extrapyramidal symptoms.

An analysis of concomitant medications use in the ITT population was not performed, because this was a negative study.

Efficacy Results
Efficacy data displays may be found in Appendices 10.3.2 to 10.3.4 of Section 10.3.

For the entire ITT population (including schizoaffective patients), for the PANSS mean change from baseline LOCF analysis, the differences were not statistically significant in favor of the protocol-specified primary comparison group (Ilo 8 mg/d + 12 mg/d) compared to placebo. The OC analysis was consistent with the LOCF analysis. Secondary LOCF analyses of the Ilo 4 mg/d, 8 mg/d and 12 mg/d groups showed that, compared to placebo, the PANSS mean change from baseline was statistically significant in favor of Ilo only for the 12 mg/d dose group, and only at Week 4 and Week 6 time points. The PANSS mean change from baseline was not statistically significant for either the Ilo 4 mg/d or Ilo 8 mg/d dose group when compared to placebo. The PANSS mean change from baseline was statistically significant in favor of the haloperidol group in the LOCF analysis from Week 2 and on and in the OC analysis at weeks 2, 3, and 4.

For the ITT population excluding schizoaffective patients, for the PANSS mean change from baseline analysis, the differences were not statistically significant for the Ilo 8 mg/d + 12 mg/d group in the LOCF analysis. The OC analysis was not performed because this was a negative study. The LOCF analyses showed a statistically significant difference compared to placebo at the $p \leq 0.05$ level for only the Ilo 12 mg/d and Hal 15 mg/d dose groups.

Conclusions
The results of Study 3000 do not provide evidence of the efficacy of iloperidone at combined doses of 8 mg/d and 12 mg/d given twice daily (primary treatment comparison) in the treatment of schizophrenia versus placebo over 42 days of treatment. Moreover, haloperidol 15 mg/d was found to be superior to placebo.

Study 3004

Investigators/Sites
Sixty six (66) investigators conducted this study at 65 sites in North America (41 in the U.S. and 3 in Canada), Africa (4 in South Africa), Europe (5 in Hungary, 7 in France, 1 in Belgium), and Australia (4). Investigators and sites are listed in Appendix 10.3.5 in Section 10.3 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial was to determine the efficacy and safety of two nonoverlapping dose ranges of iloperidone (4, 6, or 8 mg/d vs. 10, 12, or 16 mg/d) and risperidone (4, 6, or 8 mg/d) compared with placebo, administered on a twice-daily (b.i.d.) basis over 42 days in schizophrenic or schizoaffective patients with acute or subacute exacerbation.

Patient Sample
Important inclusion criteria were:

- age 18 to 65 years, inclusive

- male, surgically sterilized female, postmenopausal female, or non-pregnant female of childbearing potential who agreed not to attempt to get pregnant and to use contraception
- diagnosed with schizophrenia according to DSM-IV criteria. This included DSM-IV diagnosis of schizophrenia (i.e., 295) with suffixes 10 (disorganized), 30 (paranoid), 70 (schizoaffective), or 90 (undifferentiated)
- met criterion A symptoms of the DSM-IV schizophrenia criteria for at least the 2 weeks prior to baseline
- had PANSS Total (PANSS-T) score of at least 60 at screening and baseline. Prior to baseline evaluation and during placebo run-in, the Investigator examined the patient. If clinically relevant improvement compared with screening was detected, the placebo run-in period was extended until the patient's psychiatric status returned back to a level comparable with screening. If this improvement persisted for 7 additional days (i.e., total of 10 days of placebo run-in), the patient was not allowed to enter the study and a re-evaluation of the patient's psychiatric diagnosis was performed
- had a rating of at least "4" ("moderate") on at least 3 of the following 5 symptoms on the PANSS Positive Syndrome: delusions, conceptual disorganization, hallucinatory behavior, grandiosity and suspiciousness/persecution
- were in need of treatment with an antipsychotic medication
- had vital signs measurements within normal ranges, defined for healthy adults as supine blood pressure in the range of 100-160 mm Hg systolic and 60-95 mm Hg diastolic, with a supine radial pulse of 60-100 beats per minute (bpm)
- were medically acceptable for oral treatment with iloperidone or haloperidol, as confirmed by medical history, physical examination, electrocardiogram (ECG), and clinical laboratory tests, which were within the normal range, or, if abnormal, judged not to be clinically significant

The following were relevant exclusion criteria:

- met the DSM-IV criteria for schizophreniform disorder (295.40) or met any other primary psychiatric diagnosis (Axis I) or comorbid diagnosis (Axis II), according to DSM-IV criteria
- had diagnosis or history suggestive of chemical dependence, according to DSM-IV criteria, or toxic psychosis in the preceding 6 months, or a clinical presentation possibly confounded by the use of recreational drugs or alcohol
- were mentally retarded (moderate to severe), in a comatose state, or with significant brain trauma
- had a history of suicide attempt within the last year, or, in the opinion of the Investigator, were currently at imminent risk of suicide
- suffered from significant physical illness in the 4-week period preceding baseline
- had other medical conditions that could be expected to progress, recur, or change to such an extent that they may put the patient at special risk or bias the assessment of the clinical and the mental status of the patient to a significant degree

- had a current diagnosis or recent past history of epilepsy, major head trauma, or progressive neurological disease (other than tardive dyskinesia or drug-induced extrapyramidal side-effects)
- had past history of priapism treated with surgical intervention.
- was known to have hypersensitivity to drugs chemically related to benzisoxazoles or butyrophenones
- received during the 30 days preceding baseline any drug known to cause major organ system toxicity (e.g., chloramphenicol or tamoxifen)
- received any mood stabilizers during the 30 days preceding baseline, unless the patient was documented to have a plasma concentration below the limit of quantification.
- received electroconvulsive therapy (ECT) in the 3 months prior to baseline
- was likely to require continuous treatment with any other psychotropic drug (other than short-acting benzodiazepines), including antidepressants or mood stabilizers, during the entire study duration
- needed treatment with anticholinergic drugs during the 24 h prior to baseline evaluations (i.e., baseline day and the day before baseline) Note: Use of an anticholinergic drug on a p.r.n. basis for the treatment of extrapyramidal symptoms emerging at any other time during the study was permitted
- experienced neuroleptic malignant syndrome (rigidity/rigor, hyperpyrexia, and creatinine phosphokinase [CPK] concentrations greater than two times the upper normal limit)
- received clozapine within 60 days prior to screening
- suffered from psychotic symptoms that failed to improve (based upon the Investigator's opinion) following sufficient exposure to a therapeutic dose of any antipsychotic treatment over the last 2 years
- was previously randomized to treatment in this study or in other studies with iloperidone

Design
This was a prospective, randomized, double-blind, parallel-group, multicenter study. This study had three phases: pre-randomization, initial placebo- and risperidone-controlled double-blind (6-week), and long-term (46-week). This was followed by an open-label extension.

The pre-randomization phase consisted of a screening period and a placebo run-in period. The screening visit occurred between 3 and 30 days prior to baseline (Day 0). The single-blind placebo run-in period lasted 3 days (i.e., Days -2, -1 and 0), during which all patients were administered placebo capsules. For patients who showed clinical improvement compared to screening, the placebo run-in phase was extended (up to an additional 7 days) until the patient's psychiatric status returned back to a level comparable to that at screening.

The 6-week initial double-blind phase consisted of titration and maintenance periods. Twice daily (b.i.d.) dosing was followed throughout this phase. In the titration period (Days 1-7), fixed-dosing regimens were used whereby doses were increased up to preassigned target doses. Although patients in different treatment groups reached their target doses on different days, the titration period for all treatment groups covered the first 7 days for study design purposes. In the

maintenance period, flexible dosing regiments were used whereby patients were maintained within pre-assigned target dose ranges from Days 8-42.

After completing the initial double-blind phase, patients had the option to continue treatment in the long-term phase of the study during which patients who received iloperidone in the preceding study phase were re-started at a dose of 4 mg/d, and patients who had received placebo during the preceding phase were titrated on iloperidone 1 mg/d (Day 43), 2 mg/d (Day 44), and 4 mg/d (Day 45). Those who received risperidone during the preceding study phase were re-started at a dose of 2 mg/d risperidone. The 3-day fixed dosage titration period (Days 43-45) were followed by a flexible dosage maintenance period (Days 46-364), during which iloperidone dosages of 4-16 mg/d and risperidone dosages of 2-8 mg/d were utilized. After completing this long-term phase, patients had the option to continue treatment in the open-label extension phase.

Patients not benefiting from, or not tolerating their initial double-blind treatment after completing 28 days were permitted to enter directly into the long-term phase.

The long-term and open-label extension phases will not be discussed further in this section, due to lack of a placebo control. The dosing schedule for the pre-randomization and initial double-blind phases are summarized in the table below, extracted from the sponsor's submission.

Pre-randomization phase		Initial double-blind phase (b.i.d. dosing)	
Screening	Single-blind placebo run-in	Fixed titration	Flexible maintenance
Days -30 to -3	Days –2 to 0 [a]	Days 1 to 7	Days 8 to 42
No study medication	Pbo (b.i.d.) dosing)	Ilo low: 2→4→6 mg/d	Ilo 4, 6,[b] or 8 mg/d
		Ilo high: 2→4→8→12 mg/d	Ilo: 10, 12,[b] or 16 mg/d
		Ris: 2→4→6 mg/d	Ris: 4, 6,[b] or 8 mg/d
		Pbo	Pbo

Ilo=iloperidone; Ris=risperidone; Pbo=Placebo
[a] The placebo run-in period lasted 3 days. The last day of placebo run-in period was baseline (Day 0).
[b] Titration target dose

Patients who consented to participate in the study agreed to be hospitalized for at least 10 days (i.e., during the placebo run-in period and the titration period of the initial double-blind phase) and at any other time throughout the study, if medically indicated. The decision to discharge patients was based on the Investigator's clinical judgment and the following discharge criteria:
_ toleration of study medication
_ lack of worsening
_ absence of unmanageable behavior
_ lack of suicidal tendency
_ likelihood of compliance with the protocol, especially dosing
_ availability of a responsible caregiver

Patients were instructed to take the study medication in the morning and evening, with food, at approximately 8 a.m. and 6 p.m., respectively.

The PANSS was administered at screening, baseline, Day 7, Day 14, Day 21, Day 28, Day 35, and Day 42 or at study completion. When patients were hospitalized (i.e., during the placebo run-in period and the titration period), study assessments were done on the days indicated in the evaluation schedule. When the patients left the hospital and returned for weekly visits (i.e., during the maintenance period), a window of 3 days was allowed for flexibility in scheduling visits. The BPRS consisted of 18 items extracted from the PANSS.

Efficacy Assessments
The original protocol-defined primary efficacy variable was the Positive and Negative Syndrome Scale (PANSS) total score. No key secondary variables were identified.

On 11/30/99, the sponsor revised the primary efficacy variable from the PANSS total score to the BPRS.

Of note, the original protocol was submitted 2/18/99, and the last patient completed the study on 5/11/00.

Efficacy Analysis
The intent-to-treat (ITT) patients were those who:

- were randomized
- received at least one dose of double-blind study medication
- from whom at least one efficacy measurement was obtained while on study medication

According to the original protocol, the primary outcome measure was the change from baseline to endpoint or early termination in the Positive and Negative Syndrome Scale (PANSS) total score. The primary treatment comparison was between each of the two iloperidone dose range groups versus placebo. Hochberg's procedure was used to control the familywise Type-I error of the two comparisons: If both the iloperidone groups were significantly superior to placebo at $P \leq 0.05$, both groups will be considered efficacious. If one of the two iloperidone groups failed to reach $P \leq 0.05$, the other group had to have $P \leq 0.025$ in order to be considered as efficacious. A two-way analysis of covariance (ANCOVA) model was to be used for the analysis of treatment main effect of continuous variables based on the LOCF data set. The terms in the model included treatment, center, baseline (as covariate), and the treatment-by-baseline term. An additional analysis was performed for the exploration of treatment-by-center interaction by adding this interaction term to the above ANCOVA model. If a treatment-by-center interaction was detected, the interaction was be explored in an ad-hoc manner.

On 11/30/99, the sponsor revised the primary outcome measure to change from baseline to endpoint (Day 42 or premature termination) on the 18-item PANSS-derived BPRS. Also, the primary analysis was revised to compare the iloperidone 10-16 mg/d group with placebo. If the iloperidone 10-16 mg/d group produced statistically significant improvement over placebo,

comparison of the iloperidone 4-8 mg/d group with placebo was done to evaluate a dose-response effect. The endpoint analysis was based on the LOCF dataset using the ANCOVA model described above. The analysis to explore treatment-by-center interaction was performed on the LOCF dataset. Significant treatment-by-center interactions were investigated, if they occurred.

The original protocol was submitted 2/18/99, the last protocol amendment was submitted 7/6/00, and the last patient completed the study on 5/11/00.

Baseline Demographics
The table below displays the demographic characteristics of the randomized patient sample (excluding schizoaffective patients)[38] by treatment group. No patient under age 17 or over age 67 participated in this study. There were no major differences among the 4 treatment groups with respect to age, gender, or race.

TABLE 10.1.2 : STUDY 3004 BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS, RANDOMIZED POPULATION (EXCLUDING SCHIZOAFFECTIVE PATIENTS)[39]

	Ilo 4-8 mg/d N=123	Ilo 10-16 mg/d N=125	Risp 4-8 mg/d N=115	Placebo N=119	Total N=482
Age (yr) n					
Mean (SD)	38.5 (11.3)	38.9 (10.3)	37.2 (12.0)	37.9 (10.5)	38.1 (11.0)
Median	40.0	39.0	36.0	38.0	39.0
Min – Max	19 – 64	18 – 66	17 – 67	19 – 66	17 – 67
Sex – n (%)					
Male	88 (71.5)	89 (71.2)	92 (80.0)	85 (71.4)	354 (73.4)
Female	35 (28.5)	36 (28.8)	23 (20.0)	34 (28.6)	128 (26.6)
Race – n (%)					
Caucasian	71 (57.7)	75 (60.0)	70 (60.9)	66 (55.5)	282 (58.5)
Black	46 (37.4)	38 (30.4)	37 (32.2)	43 (36.1)	164 (34.0)
Other	6 (4.9)	12 (9.6)	8 (6.9)	10 (8.4)	36 (7.5)

[38] This information was not provided for the ITT population.
[39] This information was not provided for the ITT population.

DSM-IV diagnosis					
Disorganized	19 (15.5)	8 (6.4)	11 (9.6)	9 (7.6)	47 (9.8)
Paranoid	81 (65.9)	87 (69.6)	83 (72.2)	90 (75.6)	341 (70.8)
Undifferentiated	23 (18.7)	30 (24.0)	21 (18.3)	20 (16.8)	94 (19.5)
Baseline BPRS-total score					
N	122	125	114	118	479
Mean (SD)	55.0 (9.2)	53.3 (9.1)	54.7 (10.0)	53.7 (9.5)	54.2 (9.4)
Median	56.0	54.0	55.0	53.0	54.0
Min – Max	33 – 82	35 – 82	35 – 86	34 – 81	33 – 86

Source: Dr. Phillip Dinh, Statistical Reviewer

Baseline Severity of Illness
For the randomized patients (excluding schizoaffective patients), treatment groups had no major differences with respect to mean baseline BPRS total score[40] (mean scores of 55.0 in Ilo 4-8 mg/d patients, 53.3 in Ilo 10-16 mg/d patients, 54.7 in Risp 4-8 mg/d patients, and 53.7 in placebo patients).

Patient Disposition
Six hundred sixteen (616) patients (including schizoaffective patients) were randomized in this study. Of these patients, 613 received at least one dose of double-blind study medication and had at least one subsequent safety evaluation during Days 1-42. These patients comprised the safety population.[41] Five hundred ninety (590) patients comprised the ITT sample (143 Ilo 4-8 mg/d patients, 149 Ilo 10-16 mg/d patients, 146 Ris 4-8 mg/d patients, and 152 placebo patients). Four hundred sixty two (462) patients comprised the ITT sample excluding schizoaffective patients (115 Ilo 4-8 mg/d patients, 121 Ilo 10-16 mg/d patients, 110 Ris 4-8 mg/d patients, and 116 placebo patients).

The numbers of ITT patients (including schizoaffective patients) in-study over time are displayed in Appendix 10.3.7 in Section 10.3. At Day 42, 52% (74/143) of Ilo 4-8 mg/d patients, 58% (87/149) Ilo 10-16 mg/d patients, 60% (88/146) Ris 4-8 mg/d patients, and 40% (61/152) placebo patients completed the study.

[40] This information was not provided for the ITT population.
[41] Of note, all patients who received at least one dose of double-blind study medication also had at least one subsequent safety evaluation.

Based on the randomized population (excluding schizoaffective patients),[42] overall dropout rates were high, but there were no major differences among treatment groups [54% (66/123) of Ilo 4-8 mg/d patients, 44% (55/125) of Ilo 10-16 mg/d patients, 42% (48/115) Ris 4-8 mg/d patients, and 56% (66/119) placebo patients]. Based on the randomized population (excluding schizoaffective patients), dropout rates due to unsatisfactory therapeutic effect were highest in placebo group and lowest in the risperidone group [25% (31/123) of Ilo 10-16 mg/d patients, 21% (26/125) of Ilo 20-24 mg/d patients, 15% (17/115) of Ris 4-8 mg/d patients, and 40% (47/119) of placebo patients].

Dosing Information
Dosing information is displayed in the following table.

TABLE 10.1.3: PRESCRIBED DOSAGE (MG/D) SUMMARY STATISTICS FOR ALL RANDOMIZED PATIENTS, BY TREATMENT, DAYS 8-42 (STUDY 3004)

Exposure	Ilo 4-8 mg			Ilo 10-16 mg			Ris			Pbo		
Week	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
2	133	6.89	1.22	136	13.69	2.47	135	6.70	1.11	140	0.00	0.00
3	116	7.11	1.23	122	14.23	2.70	117	6.92	1.23	114	0.00	0.00
4	102	7.20	1.26	115	14.49	2.19	110	7.05	1.29	101	0.00	0.00
5	88	7.21	1.28	104	14.53	2.17	101	7.01	1.27	80	0.00	0.00
6	77	7.16	1.40	89	14.58	2.11	92	7.02	1.27	63	0.00	0.00

1. Based on patient's weekly mean dose, whereby daily data for each patient was aggregated over successive 7-day (weekly) intervals after baseline.
2. The Drug Administration Record (DAR) for the 1st week of the initial double-blind phase (titration period) did not capture the patient's daily dose, since this was a fixed-titration period

Concomitant Medications
All comorbid illnesses were treated in accordance with prevailing medical practice.

Antipsychotic treatment taken prior to study enrollment was discontinued in accordance with good clinical practice as described in the protocol.

Patients who were receiving chloral hydrate for insomnia, agitation, or severe restlessness prior to baseline were allowed to enter the study.

Only the following concomitant medications will be allowed for the treatment of insomnia:
• Chloral hydrate (prn, 500 mg p.o., up to 2000 mg/d total); or
• Zolpidem (prn, 5-10 mg/d p.o.)
Only three concomitant medications were allowed for the treatment of agitation or severe restlessness under the guidelines outlined in the protocol: chloral hydrate, lorazepam and sodium amytal.

The use of chloral hydrate was permitted on a p.r.n. basis at doses of 500 mg orally (up to 2000 mg/d total) during the placebo run-in period and the initial double-blind phase of the study.

[42] This information was not provided for the safety population.

The use of lorazepam (or if unavailable, another short-acting benzodiazepine) was permitted on a p.r.n. basis at doses of up to 6 mg/d p.o. for the first 2 weeks or up to 4 mg/d p.o. for the remainder of the study. Alternatively, up to 6 mg/d im (up to 3 mg/im injection) could be administered throughout the entire study. Both the oral and im formulation could be administered for up to 3 consecutive days during: 1) the placebo run-in period; 2) the first 28 days of the initial double-blind phase (a lorazepam-free period of at least 1 day must have been instituted after any 3-day treatment period with lorazepam during the first 28 days of the initial double-blind phase; and 3) no more than 1 day at a time for the remainder of the initial double-blind phase (Days 29-42).

The use of sodium amytal was permitted on a p.r.n. basis at doses of 30-50 mg/im injection (up to 3 injections/d) for up to 6 consecutive days during the placebo run-in period and the 6-week initial double-blind phase of the study.

Anticholinergic drugs for the treatment of extrapyramidal symptoms (EPS) were allowed during the placebo run-in period. However, EPS must have improved and anticholinergic medication discontinued for at least 24 h prior to the baseline day. Use of an anticholinergic drug on a p.r.n. basis for the treatment of extrapyramidal symptoms emerging during the active-treatment (double-blind) phase of the study was permitted. The Investigator reevaluated the need for anticholinergic medications on an ongoing basis. Benztropine could be initiated for extrapyramidal symptoms after randomization to active (double-blind) treatment and only after an assessment of EPS using the Extrapyramidal Symptom Rating Scale (ESRS) was completed. In case of severe EPS (e.g., acute dystonic reaction), the Investigator could treat the dystonia with a parenteral intramuscular injection of benztropine for immediate relief of symptoms, and then complete the ESRS assessment during a period when the effect of the medication was diminished, but prior to initiating treatment with oral benztropine.

Beta-blockers were not allowed during the study for any indication. Diphenhydramine hydrochloride was excluded from use in the study for a psychiatric indication or extrapyramidal symptoms.

With respect to the percentages of randomized patients[43] using various concomitant medications during the study, there were no major differences between treatment groups (80% in Ilo 4-8 mg/d patients, 82% in Ilo 10-16 mg/d patients, 79% in Ris 4-8 mg/d patients, and 81% in placebo patients), and the most frequently used were lorazepam, zolpidem, and chloral hydrate. The sponsor did not provide information regarding patients identified as protocol violators because of prohibited medication use.

Efficacy Results
Efficacy data displays may be found in Appendices 10.3.6 to 10.3.9 of Section 10.3.

[43] This information was not provided for ITT patients.

For the entire ITT population (including schizoaffective patients), for the BPRS mean change from baseline analysis, the differences were not statistically significant for the Ilo 4-8 mg/d group from Week 4 and on, for the Ilo 10-16 mg/d group from Week 3 and on, and for the Ris 4-8 mg/d group from Week 1 and on in the LOCF analysis. The OC analysis was consistent with the LOCF analysis for the Ris 4-8 mg/d group, but not for the Ilo 4-8 mg/d and Ilo 10-16 mg/d groups. For the Ilo 4-8 mg/d group, the differences were not significant at any time point and for the Ilo 10-16 mg/d group, the differences were significant at Weeks 3 and 4 only.

For the ITT population excluding schizoaffective patients, for the BPRS mean change from baseline analysis, the differences were not statistically significant for either the Ilo 4-8 mg/d group or the Ilo 10-16 mg/d group at any time point in the LOCF analysis. For the Ris 4-8 mg/d group, the differences were significant at all time points at the $p \leq 0.05$ level.

Conclusions
The results of Study 3004 do not provide evidence of the efficacy of iloperidone at flexible doses of 10 to 16 mg/d given twice daily (primary treatment comparison) in the treatment of schizophrenia versus placebo over 42 days of treatment. Moreover, risperidone 4-8 mg/d was found to be superior to placebo.

Study 3005

Investigators/Sites
Sixty seven (67) investigators conducted this study at 65 sites in North America (32 in the U.S. and 7 in Canada), Africa (1 in South Africa), Asia (3 in Israel), and Europe (5 in Poland, 6 in Hungary, 7 in Germany, 6 in Croatia). Investigators and sites are listed in Appendix 10.3.10 in Section 10.3 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial was to determine the efficacy and safety of two nonoverlapping dose ranges of iloperidone (12 or 16 mg/d and 20 or 24 mg/d) and risperidone (6 or 8 mg/d) compared with placebo, administered on a twice-daily (b.i.d.) basis over 42 days in schizophrenic or schizoaffective patients.

Patient Sample
Important inclusion criteria were:

- age 18 to 65 years, inclusive
- male, surgically sterilized female, postmenopausal female, or non-pregnant female of childbearing potential who agreed not to attempt to get pregnant and to use contraception
- diagnosed with schizophrenia according to DSM-IV criteria. This included DSM-IV diagnosis of schizophrenia (i.e., 295) with suffixes 10 (disorganized), 30 (paranoid), 70 (schizoaffective), or 90 (undifferentiated) .
- had PANSS Total (PANSS-T) score of at least 60 at screening and baseline. Prior to baseline evaluation and during placebo run-in, the Investigator examined the patient. If

clinically relevant improvement compared with screening was detected, the placebo run-in period was extended until the patient's psychiatric status returned back to a level comparable with screening. If this improvement persisted for 7 additional days (i.e., total of 10 days of placebo run-in), the patient was not allowed to enter the study and a re-evaluation of the patient's psychiatric diagnosis was performed

- had a rating of at least "4" ("moderate") on at least 3 of the following 5 symptoms on the PANSS Positive Syndrome: delusions, conceptual disorganization, hallucinatory behavior, grandiosity and suspiciousness/persecution
- was in need of psychiatric treatment
- had vital signs measurements within normal ranges, defined for healthy adults as supine blood pressure in the range of 100-160 mm Hg systolic and 60-95 mm Hg diastolic, with a supine radial pulse of 60-100 beats per minute (bpm)
- was to have no medical contraindication for oral treatment with iloperidone or risperidone, as confirmed by medical history, physical examination, electrocardiogram (ECG), and clinical laboratory tests, which were within the normal range, or, if abnormal, judged not to be clinically significant

The following were relevant exclusion criteria:

- met the DSM-IV criteria for schizophreniform disorder (295.40)
- had any other primary psychiatric diagnosis (Axis I) or comorbid diagnosis (Axis II), according to DSM-IV criteria
- had diagnosis or history suggestive of chemical dependence, according to DSM-IV criteria, or toxic psychosis in the preceding 6 months, or a clinical presentation possibly confounded by the use of recreational drugs or alcohol
- was mentally retarded (moderate to severe), in a comatose state, or with significant brain trauma
- had a history of suicide attempt within the last year, or, in the opinion of the Investigator, were currently at imminent risk of suicide
- suffered from significant physical illness in the 4-week period preceding baseline
- had other medical conditions that could be expected to progress, recur, or change to such an extent that they may put the patient at special risk or bias the assessment of the clinical and the mental status of the patient to a significant degree
- had a current diagnosis or recent past history of epilepsy, major head trauma, or progressive neurological disease (other than tardive dyskinesia or drug-induced extrapyramidal side-effects)
- had past history of priapism treated with surgical intervention.
- was known to have hypersensitivity to drugs chemically related to benzisoxazoles or butyrophenones
- received, during the 30 days immediately prior to screening, any drug known to cause major organ system toxicity (e.g., chloramphenicol or tamoxifen)
- received any mood stabilizers during the 30 days preceding baseline, unless the patient was documented to have a plasma concentration below the limit of quantification.
- received electroshock (ECT) therapy in the 3 months preceding baseline

- likely to require continuous treatment with any other psychotropic drug, including antidepressants or mood stabilizers, during the study
- required treatment with anticholinergic drugs during at least the 24 h prior to baseline evaluations (i.e., baseline day and the day before baseline) Note: Use of an anticholinergic drug on a p.r.n. basis for the treatment of extrapyramidal symptoms emerging at any other time during the study was permitted
- experienced neuroleptic malignant syndrome (rigidity/rigor, hyperpyrexia, and creatinine phosphokinase [CPK] level >2 times upper limit of normal)
- received clozapine within 60 days prior to screening
- whose psychotic symptoms failed to improve (based upon the Investigator's opinion) following sufficient exposure to a therapeutic dose of any antipsychotic treatment over the prior 2 years
- was previously randomized to treatment in this study or in other studies with iloperidone

Design
This was a prospective, randomized, double-blind, placebo- and risperidone-controlled, multicenter study. This study has three phases: pre-randomization, short-term double-blind (6-week), and long-term open-label (46-week).

The dosing schedule for the pre-randomization and short-term double-blind phases are summarized in the table below, extracted from the sponsor's submission.

Pre-randomization phase		Short-term double-blind phase (bid dosing)	
Day -30 to -3	Day -2 to 0[a]	Day 1 to 7	Day 8 to 42
Screening	Single blind placebo run-in period (bid dosing)	Fixed titration period (mg/d)	Flexible maintenance period (mg/d)
	Placebo	Ilo low: 2→4→8→12	Ilo low: 12[b] or 16
		Ilo high:2→4→8→12→ 16→20	Ilo high: 20[b] or 24
		Pbo	Pbo
		Ris: 2→4→6	RIS: 6[b] or 8

Ilo=iloperidone; Ris=risperidone; Pbo=placebo
[a] Placebo run-in period lasted a minimum of 3 days; the last day of placebo run-in period was baseline (Day 0)
[b] Titration target dose

Patients who consented to participate in the study agreed to be hospitalized for at least 10 days (i.e., during the placebo run-in period and the titration period of the initial double-blind phase) and at any other time throughout the study, if medically indicated. The decision to discharge patients was based on the Investigator's clinical judgment and the following discharge criteria:
_ toleration of study medication
_ lack of worsening

_ absence of unmanageable behavior
_ lack of suicidal tendency
_ likelihood of compliance with the protocol, especially dosing
_ availability of a responsible caregiver

Patients were instructed to take all study medication (3 tablets and 1 capsule) in the morning and evening, at approximately 8 AM and 6 PM, respectively. Study medication was to be taken with food.

Initially patients were randomized to one of three treatment groups in a 2:1:1 ratio (iloperidone 12-16 mg/d, risperidone, and placebo, respectively). When it was determined that patients might benefit from iloperidone doses >16 mg/d (based on the outcome of Study 3004), randomization to iloperidone 20-24 mg/d (10 to 12 mg bid) was initiated after approximately one-half of the anticipated enrollment was completed. From that point on, patients were randomized in a ratio of 1:2:1:1 to receive treatment with iloperidone 12-16 mg/d, iloperidone 20-24 mg/d, risperidone, or placebo to balance the treatment arms.

For the iloperidone 12-16 mg/d group, the dosage was increased every other day until the target dosage of 12 mg/d was reached on Day 7. For the 20-24 mg/d group, daily dosage increases were made up of 12 mg/d (Days 4 and 5). Thereafter, the dosage was increased every day until the target dose of 20 mg/d was reached on Day 7.

The target dose during titration was the lower of the dosages (Level A) in each treatment group. The investigator was given the option of increasing the dosage to a higher maintenance dose (Level B) in order to explore additional benefit. Thus, if randomized to iloperidone 12 mg/d (Level A), the dosage could be increased to 16 mg/d (Level B); if randomized to iloperidone 20 mg/d iloperidone (Level A), an increase to 24 mg/d (Level B) was allowed, and if randomized to risperidone, an increase from 6 to 8 mg/d was permitted.

Patients who completed 42 days of double-blind treatment were eligible to participate in the long-term open-label phase of the study. The following description of the open-label phase is based on the sponsor's protocol. The long-term open-label phase consisted of a blinded fixed titration period followed by an open label maintenance flexible dosing period. The fixed titration period lasted for 7 days (Days 43 to Day 49), and the flexible maintenance dosing period lasted from Day 50 (Week 8) through Day 364 (Week 52).

An overview of study design including the prerandomization, short-term double-blind and long-term open-label phases of the study is provided in the table below, extracted from the sponsor's submission.

Prerandomization phase		Short-term double-blind phase (b.i.d. dosing)		Long-term open-label phase (q.d. dosing)	
Day -30 to -3	Day -2 to 0[a]	Day 1 to 7	Day 8 to 42	Day 43 to 49	Day 50 to 364
Screening	Single blind placebo run-in period (b.i.d. dosing)	Fixed titration period (mg/d)	Flexible maintenance period (mg/d)	Fixed titration period (mg/d)	Flexible maintenance period (mg/d)
	P	ILO low: 2→4→8→12	ILO low: 12[b] or 16	ILO low: 8	ILO: 4/L, 8/M, 12/N, 16/O or 24/P
		ILO high: 2→4→8→12→16→20	ILO high: 20[b] or 24	ILO high: 8	
		P	P	ILO: 2→4→8	
		RIS: 2→4→6	RIS: 6,[b] or 8	ILO: 2→4→8	

Abbreviations: P=placebo; ILO=iloperidone; RIS=risperidone; mg/d=milligrams/day; b.i.d.=twice daily; q.d.=once daily
a The placebo run-in period will last at least 3 days. The last day of placebo run-in period will be baseline (Day 0).
b Titration target dose

During the fixed-dose period of the open label phase, all patients received treatment with iloperidone and all dosing switched from twice to once daily. Patients who received iloperidone during the short-term double-blind phase continued to receive iloperidone at a fixed dose of 8 mg/d (dose level M), given q.d.

Patients who received either placebo or risperidone during the short-term double-blind phase were switched to iloperidone and their medication were titrated using a fixed titration schedule. These patients achieved their target dose of 8 mg/d (dose level M) on Study Day 47. All patients remained at dose level M through Study Day 49.

Patients were switched to open-label treatment on Day 50, the first day of the long-term maintenance period.

The long-term open-label phase will not be discussed further in this section, due to lack of a placebo control.

The PANSS was administered at screening, baseline, Day 7, Day 14, Day 21, Day 28, Day 35, and Day 42 or at study completion. When patients were hospitalized (i.e., during the placebo run-in period and the titration period), study assessments were done on the days indicated in the evaluation schedule. When the patients left the hospital and returned for weekly visits (i.e., during the maintenance period), a window of 3 days was allowed for flexibility in scheduling visits.

Efficacy Assessments
The protocol-defined primary efficacy variable was the 18-item PANSS-derived BPRS. No key secondary variables were identified.

Efficacy Analysis
The intent-to-treat (ITT) patients were those who:

- were randomized
- received at least one dose of double-blind study medication

- from whom at least one efficacy measurement was obtained while on study medication

The primary outcome measure was the change from baseline to endpoint or early termination in the 18-item BPRS extracted from the Positive and Negative Syndrome Scale (PANSS). In order to control for multiplicity in the analyses of efficacy, the primary comparison was between the iloperidone 12 to 16 mg range and placebo. If this test was significant at alpha=0.05, the subsequent pairwise comparisons of iloperidone 20 to 24 mg dose range to placebo would be considered significant at the 0.05 level. If the comparison of 12 to 16 mg range to placebo was not significant, comparison of the 20 to 24 mg range to placebo would not be considered significant regardless of the nominal significance level. A two-way analysis of covariance (ANCOVA) model was used for the analysis of treatment main effect of continuous variables. The terms in the model include treatment, center, baseline (as covariate), and the treatment-by-baseline term. An additional analysis was performed for the exploration of treatment-by-center interaction by adding this interaction term to the above ANCOVA model. If a treatment-by-center interaction was detected, the interaction will be explored in an ad-hoc manner. Categorical variables were analyzed using Cochran-Mantel-Haenszel (CMH) test blocking on centers.

The primary efficacy analysis was the analysis of the primary variable using the ANCOVA model based on the LOCF data set of the short-term double-blind phase. The analysis to explore treatment-by-center interaction was performed on the LOCF data set. Significant treatment-by-center interactions were investigated.

Of note, the last protocol amendment 2/14/01 and the last patient completed the study on 3/15/01. The undersigned reviewer reviewed the protocol amendments and determined that they were not likely to have a significant impact on the efficacy results.

Baseline Demographics
The table below displays the demographic characteristics of the randomized patient sample (excluding schizoaffective patients)[44] by treatment group. No patient under age 18 or over age 65 participated in this study. There were no major differences among the 4 treatment groups with respect to age, gender, or race.

[44] This information was not provided for the ITT population.

TABLE 10.1.4 : STUDY 3005 BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS, RANDOMIZED POPULATION[45]

	Ilo 12-16 mg/d N= 188	Ilo 20-24 mg/d N= 114	Risp 6-8 mg/d N= 126	Placebo N=120	Total N= 548
Age (yr) n					
Mean (SD)	39.0 (11.4)	36.1 (10.9)	40.0 (10.7)	38.4 (10.4)	38.5 (11.0)
Median	38.0	36.0	39.5	38.0	38.0
Min – Max	18 – 65	19 – 65	18 – 64	18 – 64	18 – 65
Sex – n (%)					
Male	120 (63.8)	84 (73.7)	78 (61.9)	75 (62.5)	357 (65.2)
Female	68 (36.2)	30 (26.3)	48 (38.1)	45 (37.5)	191 (34.8)
Race – n (%)					
Caucasian	129 (68.6)	79 (69.3)	97 (77.0)	82 (68.3)	387 (70.6)
Black	53 (28.2)	27 (23.7)	21 (16.7)	30 (25.0)	131 (23.9)
Other	6 (3.2)	8 (7.0)	8 (6.3)	8 (6.7)	30 (5.5)
Baseline BPRS-total score					
N	186	113	123	120	542
Mean (SD)	54.6 (7.5)	55.3 (8.5)	55.7 (8.6)	55.3 (8.6)	55.2 (8.2)
Median	54.5	55.0	55.0	55.0	55
Min – Max	39 – 79	39 – 85	38 – 92	35 – 90	35 – 92

Source: Dr. Phillip Dinh, Statistical Reviewer

Baseline Severity of Illness
For the randomized patients (excluding schizoaffective patients), treatment groups had no major differences with respect to mean baseline BPRS total score[46] (mean scores of 54.6 in Ilo 12-16 mg/d patients, 55.3 in Ilo 20-24 mg/d patients, 55.7 in Risp 6-8 mg/d patients, and 55.3 in placebo patients).

[45] This information was not provided for the ITT population.
[46] This information was not provided for the ITT population.

Patient Disposition
Seven hundred six (706) patients (including schizoaffective patients) were randomized in this study. Of these patients, 697 received at least one dose of double-blind study medication and had at least one subsequent safety evaluation during Days 1-42. These patients comprised the safety population.[47] Six hundred seventy one (671) patients comprised the ITT sample (230 Ilo 12-16 mg/d patients, 141 Ilo 20-24 mg/d patients, 148 Ris 6-8 mg/d patients, and 152 placebo patients). Five hundred twenty one (521) patients comprised the ITT sample excluding schizoaffective patients (178 Ilo 12-16 mg/d patients, 111 Ilo 20-24 mg/d patients, 119 Ris 6-8 mg/d patients, and 113 placebo patients).

The numbers of ITT patients (including schizoaffective patients) in-study over time are displayed in Appendix 10.3.12 in Section 10.3. At Day 42, 57% (131/230) of Ilo 12-16 mg/d patients, 61% (86/141) of Ilo 20-24 mg/d patients, 76% (112/148) of Ris 6-8 mg/d patients, and 55% (84/152) of placebo patients completed the study. Of note, the number of patients completing the study based on the sponsor's data displayed in Appendix 10.3.12 (obtained from Post-test Table 9.1-2 on page 592 of 36408 of the sponsor's CSR for Study 3005) is not consistent with the data contained in Table 7-2 on page 62 of 36408 of the sponsor's CSR for Study 3005.

For the ITT population excluding schizoaffective patients, at Day 42, 57% (102/178) of Ilo 12-16 mg/d patients, 65% (72/111) of Ilo 20-24 mg/d patients, 77% (92/119) of Ris 6-8 mg/d patients, and 53% (60/113) placebo patients completed the study.

Based on the randomized population (excluding schizoaffective patients),[48] overall dropout rates were high, but were lowest in the Ris 6-8 mg/d group [47% (88/188) of Ilo 12-16 mg/d patients, 37% (42/114) of Ilo 20-24 mg/d patients, 28% (35/126) of Ris 6-8 mg/d patients, and 48% (57/120) of placebo patients]. Based on the randomized population (excluding schizoaffective patients), dropout rates due to unsatisfactory therapeutic effect was lowest in the risperidone group [27% (51/188) of Ilo 12-16 mg/d patients, 19% (22/114) Ilo 20-24 mg/d patients, 8% (10/126) Ris 6-8 mg/d patients, and 31% (37/120) placebo patients].

Dosing Information
Dosing information is displayed in the following table.

[47] Of note, all patients who received at least one dose of double-blind study medication also had at least one subsequent safety evaluation.
[48] This information was not provided for the safety population.

TABLE 10.1.5: PRESCRIBED DOSAGE (MG/D) SUMMARY STATISTICS FOR ALL RANDOMIZED PATIENTS, BY TREATMENT, DAYS 8-42 (STUDY 3005)

Exposure	Ilo 12-16 mg			Ilo 20-24 mg			Ris			Pbo		
Week	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
2	206	13.80	2.01	127	21.42	2.42	145	6.76	1.13	138	0.00	0.00
3	170	14.09	2.20	107	21.69	2.87	134	6.92	1.04	121	0.00	0.00
4	154	14.38	2.21	98	22.27	1.97	124	7.05	1.01	103	0.00	0.00
5	141	14.48	1.94	92	22.11	2.26	119	7.05	1.04	93	0.00	0.00
6	138	14.42	2.06	87	22.17	2.10	114	7.09	1.06	88	0.00	0.00

Notes:
1. Based on patient's weekly mean dose, whereby daily data for each patient was aggregated over successive 7-day (weekly) intervals after baseline.
2. The Drug Administration Record (DAR) for the 1st week of the short-term double-blind phase (titration period) did not capture the patient's daily dose, since this was a fixed-titration period

Concomitant Medications
All comorbid illnesses were treated in accordance with prevailing medical practice.

Medications with known central nervous system effects that were likely to interfere with study assessments (e.g., antidepressants, anxiolytics, mood stabilizers, sedative/hypnotics, or psychostimulants) were prohibited during the study.

Antipsychotic treatment taken prior to study enrollment were discontinued according to the following criteria:

- patients who had not recently received treatment with a neuroleptic had a placebo run-in period of 3 days
- patients who had recently received treatment with an oral neuroleptic had a placebo run-in period of 3 days, or longer, if appropriate.
- Patients who were being treated with a depot neuroleptic had to complete their entire treatment cycle prior to beginning the 3-day placebo run-in
- Patients who showed clinical improvement during the placebo run-in period had an extension of this period up to a maximum of 14 days. Patients were randomized only after reaching a psychiatric status comparable to screening.

Patients who received allowed medication for insomnia, agitation, or severe restlessness prior to baseline were permitted to enter the study.

The following concomitant medications were permitted for the placebo run-in period and the short-term double-blind phase of the study for the treatment of insomnia:
• Chloral hydrate (prn, 500 mg p.o., up to 2000 mg/d total); or
• Zolpidem (prn, 5-10 mg/d p.o.). In countries where zolpidem was not available, another short half-life hypnotic was acceptable.

No study evaluation was permitted until at least 4 hours after the administration of either of the above medications.

Only two concomitant medications were allowed for the treatment of agitation or severe restlessness under the guidelines outlined in the protocol: chloral hydrate or lorazepam.

The use of chloral hydrate was permitted on a p.r.n. basis at doses of 500 mg orally (up to 2000 mg/d total) during the placebo run-in period and the initial double-blind phase of the study.

The use of lorazepam (or if unavailable, another short-acting benzodiazepine) was permitted on a p.r.n. basis at doses of up to 6 mg/d p.o. for the first 2 weeks or up to 4 mg/d p.o. for the remainder of the study. Alternatively, up to 6 mg/d im (up to 3 mg/im injection) may have been administered throughout the entire study. In countries where lorazepam IV/im was not available, another injectable short half-life benzodiazepine was acceptable. Both the oral and im formulation were allowed in 3-day consecutive periods. At the end of each 3-day period the patient was evaluated for a decrease or discontinuation of the dose of lorazepam.

No study evaluation was permitted until at least 4 hours after the administration of either of the above medications.

Anticholinergic drugs for the treatment of extrapyramidal symptoms (EPS) were allowed during the placebo run-in period. However, EPS must have improved and anticholinergic medication discontinued for at least 24 h prior to the baseline day. Use of an anticholinergic drug on a p.r.n. basis for the treatment of extrapyramidal symptoms emerging during the active-treatment phase of the study was permitted. The Investigator reevaluated the need for anticholinergic medications on an ongoing basis. Benztropine was the only medication allowed for the treatment of extrapyramidal symptoms emerging after randomization to active treatment (double-blind phase) and only after an assessment of EPS using the Extrapyramidal Symptom Rating Scale (ESRS) was completed. In case of severe EPS (e.g., acute dystonic reaction), the Investigator was permitted to treat the dystonia with a parenteral intramuscular injection of benztropine for immediate relief of symptoms, then complete the ESRS assessment during a period when the effect of the medication was diminished, but prior to initiating treatment with oral benztropine mesylate.

Beta-blockers were not permitted during the study for any indication. Diphenhydramine hydrochloride was excluded from use in the study for a psychiatric indication or extrapyramidal symptoms.

With respect to the percentages of randomized patients[49] using various concomitant medications during the study, there were no major differences between treatment groups (66% in Ilo 12-16 mg/d patients, 67% in Ilo 20-24 mg/d patients, 73% in Risp 6-8 mg/d patients, and 69% in placebo patients), and the most frequently used were lorazepam, paracetamol, zolpidem, and chloral hydrate. Five (1%) patients in the iloperidone group, 3 (2%) patients in the risperidone group, and 1 patient in the placebo group were withdrawn from the study prematurely due to protocol deviations. The sponsor did not provide information regarding patients identified as protocol violators because of prohibited medication use.

[49] This information was not provided for ITT patients.

Efficacy Results
Efficacy data displays may be found in Appendices 10.3.11 to 10.3.16 of Section 10.3.

For the BPRS mean change from baseline analysis (excluding schizoaffective patients), compared with placebo, the differences were statistically significant for risperidone from Week 1 onward, for the Ilo 12-16 mg/d group from Week 3 onward, and for the Ilo 20-24 mg/d group from Week 3 onward in the LOCF analysis. The OC analysis at Week 6 was consistent with the LOCF analysis. The OC analysis by week was not available.

When stratified by entering date of the iloperidone 20-24 mg/d group (since this dose group was added midway through enrollment), the results were roughly comparable.

Conclusions
The results of Study 3005 provide evidence that suggests efficacy of iloperidone at flexible doses of 12 to 16 mg/d and 20 to 24 mg/d given twice daily in the treatment of schizophrenia versus placebo over 42 days of treatment. However, risperidone 6-8 mg/d had a larger effect size[50] and appeared to have an earlier onset of action than both the iloperidone dose groups (12-16 mg/d and 20-24 mg/d).

Study 3101

Investigators/Sites
Forty one investigators conducted this study at 35 sites in the U.S. and 9 sites in India. Of note, on 11/9/05, the sponsor modified participating sites from U.S., Mexico, Canada and Singapore to U.S. and India. Investigators and sites are listed in Appendix 10.3.17 in Section 10.3 extracted from the sponsor's submission.

Objectives
According to the original protocol submitted on 8/2/05, the objective of this trial was to 1) evaluate the efficacy of a 24 mg/day iloperidone dose compared to placebo, administered b.i.d. over 28 days to schizophrenic patients and 2) to assess the efficacy of a 24 mg/d (12 mg b.i.d.) iloperidone dose in schizophrenic patients lacking the CNTF FS63Ter mutation versus patients who harbor the mutation.

In a 9/16/05 protocol amendment, the study objectives were revised to allow for a step-down approach in which the second primary objective would only be evaluated if significance was attained on the first primary objective of the study. In addition, the second primary objective was changed to "to assess the efficacy of treatment of iloperidone on patients with schizophrenia

[50] The larger effect size in the risperidone group appears to be statistically significant for the 12-16 mg/d dose group and not for the 20-24 mg/d dose group in a post-hoc analysis. However, the study was not designed to compare active control to iloperidone and this finding is difficult to interpret.

lacking the CNTF FS63Ter polymorphism compared with all patients with schizophrenia treated with placebo."

In an 8/4/06 protocol amendment, the step-down primary objective was modified to reflect an analysis in which comparisons are made among the same subpopulation of patients (i.e., patients in the genetic subgroup receiving iloperidone with those in the same genetic subgroup receiving placebo). Thus, the step-down objective was changed to read "to assess the efficacy of a 24 mg/d (12 mg b.i.d.) iloperidone dose in patients with schizophrenia lacking the *CNTF FS63Ter* polymorphism compared with patients with schizophrenia treated with placebo lacking the *CNTF FS63Ter* polymorphism."

Of note, the last patient completed the study on 9/26/06.

Patient Sample
Important inclusion criteria were:

- age 18 to 65 years, inclusive. Patients older than 65 years were considered on a case-by-case basis.
- male, surgically sterilized female, postmenopausal female, or non-pregnant female of childbearing potential who agreed not to attempt to get pregnant and to use contraception
- BMI >18 and <35 kg/m^2; patients with BMI>35 were considered on a case-by-case basis, after discussion with the Medical Monitor
- had a diagnosis of schizophrenia according to DSM-IV criteria. This included DSM-IV diagnoses of schizophrenia (i.e., 295) with suffixes 10 (disorganized), 30 (paranoid), or 90 (undifferentiated). Of note, according to the original protocol submitted 8/2/05, the sponsor's inclusion criteria included a diagnosis of schizoaffective disorder. This diagnosis of schizoaffective disorder was removed from the inclusion criteria on 9/16/05.
- had a CGI-S of at least 4 at baseline
- had a PANSS Total (PANSS-T) score of at least 70 at screening and baseline
- had a rating of at least "4" ("moderate") on at least 2 of the following 4 PANSS Positive (PANSS-P) symptoms: delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution at screening and baseline
- was in need of psychiatric treatment
- had no medical contraindication for oral treatment with iloperidone as confirmed by medical history, physical examination, electrocardiogram (ECG), and clinical laboratory tests, which were within the normal range, or, if abnormal, judged not to be clinically significant.

The following were relevant exclusion criteria:

- met the DSM-IV criteria for schizophreniform disorder (295.40) and schizoaffective disorder (295.70)
- any other primary psychiatric diagnosis (Axis I) or any axis to interfere with compliance to the protocol

- had diagnosis or history suggestive of chemical dependence, according to DSM-IV criteria, or toxic psychosis in the preceding 6 months, or a clinical presentation possibly confounded by the use of recreational drugs or alcohol
- was hospitalized more than 14 days immediately prior to screening
- was mentally disabled (moderate to severe)
- had significant brain trauma or a coma lasting more than 24 hours
- currently at imminent risk of harm to self or others
- had a positive test result on urine drug screen (at the screening visit) for amphetamines cocaine, phencyclidine, or opiates
- suffered from significant physical illness in the 4-week period preceding baseline
- had other medical conditions that could be expected to progress, recur, or change to such an extent that they may put the patient at special risk or bias the assessment of the clinical and the mental status of the patient to a significant degree
- known congenital long QT syndrome
- current diagnosis or past history of epilepsy, major head trauma, or progressive neurological disease (other than tardive dyskinesia or drug-induced EPS)
- past history of priapism that required treatment with surgical intervention
- known to have hypersensitivity to drugs chemically related to benzisoxazoles or butyrophenones
- treated with a long-acting injectable antipsychotic within one treatment cycle of screening
- received, during the 30 days preceding baseline, any drug known to cause major organ system toxicity (e.g., chloramphenicol or tamoxifen)
- received electroshock in the 3 months preceding baseline
- likely to require continuous treatment with any other psychotropic drug, including antidepressants or mood stabilizers, during the entire study duration
- experienced neuroleptic malignant syndrome (rigidity/rigor, hyperpyrexia, and creatinine phosphokinase [CPK] concentrations greater than two times the upper normal limit)
- history of treatment with clozapine
- had psychotic symptoms that failed to improve (based upon the Investigator's opinion) following sufficient exposure to a therapeutic dose of any antipsychotic treatment over the last 2 years
- was previously randomized to treatment in this study or in other studies with iloperidone within the last 4 years

Design

This was a prospective, randomized, double-blind, placebo- and ziprasidone-controlled, parallel-group, multicenter study. This study had 3 phases: the pre-randomization; short-term, double-blind; and long-term, open-label phase. The following table, extracted from the sponsor's submission, summarizes the study design for the pre-randomization and short-term, double-blind phases.

Pre-randomization phase		**Short-term double-blind phase (b.i.d. dosing)**	
Screening visit	Baseline visit	Titration period (mg/d)	Maintenance period (mg/d)
Days -14 to -3	Day 0	Days 1 to 7	Days 8 to 28
		iloperidone 2→4→8→12→16→20→24	iloperidone 24
		placebo	placebo
		ziprasidone 40→40→80→80→120→120→160	ziprasidone 160

All patients who completed the short-term, double-blind phase had the option of continuing treatment in the long-term, open-label phase with iloperidone for an additional 175 days. Due to lack of a placebo control, the long-term open label phase will not be discussed further in this section.

All patients were to be hospitalized during the 4 weeks of the short-term, double-blind study (Days 1 to 28). Day passes could be allowed at the Investigator's discretion during Weeks 3 and 4 to patients who had a responsible caregiver who could provide a stable residence. This information was to be documented in the source documents. On Weeks 3 and 4, three day passes were allowed for each week (maximum of 6 passes total). These passes could not be granted in consecutive days (e.g., a patient was not able to receive a weekend pass for Saturday and Sunday).
Patients who were granted day passes were required to be at the hospital for dosing. Caregivers were advised to follow all of the protocol requirements. Patients could have unlimited supervised outings with study staff personnel during Weeks 2 to 4. One emergency supervised outing could be granted by the Investigator during Week 1, if needed.

The PANSS was administered at screening, baseline, Day 7, Day 10, Day 14, Day 21, and Day 28 or at early termination. A window of ±1 day was allowed for flexibility in scheduling visits. Deviations from the specified screening and baseline time window were allowed if permitted by Vanda. Day 10 visit was to be conducted at least 2 days after Day 7 visit.

Efficacy Assessments
The protocol-defined primary efficacy variable was the Positive and Negative Syndrome Scale (PANSS) total score. No key secondary variables were identified.

Efficacy Analysis
Per the original protocol, the ITT patients were those who:
- were randomized
- received at least one dose of double-blind study medication

- from whom at least one post-baseline efficacy measurement was obtained while on study medication

The modified intent-to-treat (ITT) patients were those who:

- were randomized
- received at least one dose of double-blind study medication
- from whom a baseline PANSS score was obtained
- from whom at least one post-baseline PANSS efficacy measurement was obtained while on study medication

All efficacy analyses were conducted on the modified ITT population, the primary study population.

According to the original protocol, the primary efficacy variable was the slope of the regression line from baseline to the last scheduled observation in the PANSS total score, to be analyzed utilizing a linear MMRM model.

In a 9/16/05 protocol amendment, the sponsor changed the primary efficacy variable to the change from baseline to the last scheduled observation in the PANSS-T score. Also, unsatisfactory therapeutic effect was added as an acceptable reason for early withdrawal. The primary efficacy variable was the change from baseline to the last scheduled observation (Day 28) in the PANSS-T score, which was to be analyzed using a mixed-model repeated measures (MMRM) model. In order to control for multiplicity in the analysis of efficacy, if the primary objective was significant at alpha=0.05, a step-down primary objective was tested. The step-down primary objective of this study was to determine the efficacy of iloperidone 24 mg/d in patients with the *CNTF FS63Ter(-)* genotype compared to placebo-treated patients with the *CNTF FS63Ter(-)* genotype as measured by the PANSS-T score.

Analyses were adjusted for heterogeneity at baseline and heterogeneity among centers.

The MMRM analysis used the observed case (OC) dataset for all scheduled visits already mapped and, if unscheduled or early termination assessments occurred subsequent to scheduled assessment, then this value was carried forward to the missing next scheduled visit (but did not carry beyond that next scheduled visit to the end of the study).

A basic analysis of variance (ANOVA) model was fitted to assess treatment differences in PANSS-T score at baseline, with main effect terms for treatment (iloperidone vs. placebo) for the primary efficacy objective and pooled site.

Of note, the date of the original protocol was 8/2/05; the last protocol amendment, which included significant changes in study's objective, was submitted on 8/4/06; and the last patient completed the study on 9/26/06.

Baseline Demographics
The table below displays the demographic characteristics of the randomized patient sample[51] by treatment group. No patient under age 18 or over age 65 participated in this study. There were no major differences among the 3 treatment groups with respect to age, gender, or race.

TABLE 10.1.6 : STUDY 3101[52]
BASELINE DEMOGRAPHICS, RANDOMIZED POPULATION[53]

Treatment (n)	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Asian	Other
Iloperidone 24 mg/d (295)	39.5	18-65	83	17	38	50	8	4
Ziprasidone 160 mg/d (149)	40.0	20-61	76	24	34	51	8	7
Placebo (149)	40.7	19-64	76	23	31	51	10	8

Baseline Severity of Illness
For the randomized patients, treatment groups had no major differences with respect to mean baseline PANSS total score[54] (mean scores of 92.67 in iloperidone 24 mg/d patients, 90.95 in ziprasidone 160 mg/d patients, and 90.32 in placebo patients).

Patient Disposition
Of the 606 patients assigned to randomization, 593 patients were randomized to the study. Thirteen patients initially assigned to randomization were randomized in error, either randomization at a second site after an initial randomization or randomization following screening failure.

597 patients received at least 1 dose of double-blind study medication and had at least 1 subsequent safety evaluation during Days 1-28. These patients were included in the safety analysis.[55] Five hundred sixty seven (567) patients comprised the ITT sample (283 iloperidone 24 mg/d patients, 144 ziprasidone 160 mg/d patients, and 140 placebo patients).

[51] This information was not provided for the ITT population.
[52] Figures may not add up to 100% due to rounding.
[53] This information was not provided for the ITT population.
[54] This information was not provided for the ITT population.
[55] Of note, all patients who received at least one dose of double-blind study medication also had at least one subsequent safety evaluation.

The numbers of ITT patients in-study over time are displayed in Appendix 10.3.19 in Section 10.3. At Day 28, 65% (193/295) iloperidone 24 mg/d patients, 66% (98/149) ziprasidone 160 mg/d patients, and 60% (90/149) placebo patients completed the study. Based on the randomized population,[56] there were no major differences in overall dropout rates among treatment groups [35% (102/295) iloperidone 24 mg/d patients, 34% (51/149) ziprasidone 160 mg/d patients, and 40% (59/149) placebo patients]. Based on the randomized population, the dropout rate due to unsatisfactory therapeutic effect was higher in placebo patients [7% (21/295) iloperidone 24 mg/d patients, 8% (12/149) ziprasidone 160 mg/d patients, and 13% (19/149) placebo patients].

Dosing Information
This was a fixed dose study.

Concomitant Medications
All comorbid illnesses were treated in accordance with prevailing medical practice.

Medications with known central nervous system effects (e.g., antidepressants, anxiolytics, mood stabilizers, sedative/hypnotics, or psychostimulants), which were likely to interfere with study assessments, were prohibited during the study. The last dose of prior antipsychotic medication was to be on Day -1. No additional washout period for prior antipsychotic medication was required before study drug was administered on Day 1. With the exception of study drug, no use of antipsychotic medication was allowed during the short-term, double-blind phase.

Patients were allowed to receive the medications outlined below for the treatment of insomnia, agitation, or severe restlessness before and during the study:

For the treatment of insomnia, only zolpidem (p.r.n., 5 to 10 mg/d p.o.) was permitted. In countries where zolpidem was not available, another nonbenzodiazepine with a short half-life was permitted. If this medication was administered to a patient, a minimum of 8 hours had to elapse prior to completing efficacy evaluations.

For the treatment of agitation or severe restlessness, only lorazepam was permitted. During Days 1 to 3, a dose of lorazepam was to be administered prior to bedtime. In addition, the Investigator was allowed to administer lorazepam on a standing p.r.n. basis at doses of up to 10 mg/d orally. During Days 4 to 14, the Investigator was permitted to administer lorazepam on a p.r.n. basis at doses of up to 8 mg/d orally. During Days 15 to 28, the Investigator could administer up to 6 mg/d dose of lorazepam orally on a p.r.n. basis. Alternatively, the Investigator could administer lorazepam up to 6 mg/d intramuscularly (i.m.) (up to 3 mg/i.m. injection) throughout the entire study. In countries where lorazepam (i.m.) was not available, another injectable (i.m.) benzodiazepine with a short half-life was acceptable. Both the oral and i.m. formulation could have been administered in 3-day consecutive periods. At the end of each 3-day period, the patient was evaluated for a decrease in the dose of lorazepam or the initiation of a

[56] This information was not provided for the safety population.

lorazepam-free period. If this medication was administered, a minimum of 4 hours had to elapse prior to completing the efficacy evaluations.

Use of an anticholinergic drug on a p.r.n. basis for the treatment of EPS that emerged during the active-treatment phase of the study was permitted. The Investigator was to reevaluate the need for anticholinergic medications on an ongoing basis. Benztropine mesylate treatment (or the equivalent, if benztropine mesylate was not available) was allowed for the treatment of EPS after randomization to active treatment and only after an assessment of EPS by Extrapyramidal Symptom Rating Scale (ESRS) examination was completed. In the case of severe EPS (e.g., acute
dystonic reaction), the Investigator was permitted to treat the dystonia with a parenteral i.m. injection of benztropine mesylate or equivalent for immediate relief of symptoms, then complete an ESRS during the period when the effect of the medication was diminished, but prior to initiating treatment with oral benztropine mesylate, if necessary. In the event that any of the above-mentioned medication was used in the treatment of insomnia, agitation, severe restlessness, or EPS, the Investigator was required to record this information on the Concomitant Medications Form on the CRF.

With respect to the percentages of randomized population patients[57] using various concomitant medications during the study, there were no major differences between treatment groups (93% in iloperidone 24 mg/d patients, 96% in ziprasidone 160 mg/d patients, and 91% in placebo patients). The most frequently used were acetaminophen; antacids, other combinations; lorazepam; clonazepam; zolpidem; benztropine; and ibuprofen. Notable differences among treatment groups and notable concomitant medications are listed in the following table:

TABLE 10.1.7: CONCOMITANT MEDICATIONS, BY TREATMENT, SHORT-TERM DOUBLE BLIND PHASE (DAYS 1-28), RANDOMIZED POPULATION

	Iloperidone N=295	Ziprasidone N=149	Placebo N=149
Quetiapine	8 (2.7%)	9 (6.0%)	5 (3.4%)
Olanzapine	4 (1.4%)	7 (4.7%)	6 (4.0%)
Ziprasidone	1 (0.3%)	4 (2.7%)	1 (0.7%)
Fluphenazine	3 (1.0%)	1 (0.7%)	1 (0.7%)
Thorazine	0 (0%)	1 (0.7%)	0 (0%)
Haloperidol	4 (1.4%)	5 (3.4%)	2 (1.3%)
Benztropine	36 (12.2%)	23 (15.6%)	11 (7.4%)
Risperidone	16 (5.4%)	5 (3.4%)	11 (7.4%)
Aripiprazole	1 (0.3%)	2 (1.3%)	5 (3.4%)

[57] This information was not provided for the MITT population.

Thus, a total of 13% (37/295) Ilo patients, 23% (34/149) Zip patients, and 21% (31/149) Pbo patients received concomitant antipsychotic medications. Per a 6/4/08 email from Dr. Phillip Dinh, Statistical reviewer, it is difficult to tell whether or not removing these patients from the database would have a negative impact on this study's efficacy results.

Two (2%) patients in the iloperidone group, 1 (2%) patient in the ziprasidone group, and 1 (1.7%) patient in the placebo group were withdrawn from the study prematurely due to protocol deviations. The sponsor did not provide an enumeration of patients identified as protocol violators because of prohibited medication use.

Efficacy Results
Efficacy data displays may be found in the Appendices 10.3.18 to 10.3.20 in Section 10.3.

For the PANSS mean change from baseline analysis, compared with placebo, the differences between adjusted mean change from baseline were statistically significant in favor of ziprasidone from Day 10 onward and in favor of iloperidone from Day 21 onward for the MMRM analysis. For the OC analysis, the differences between mean change from baseline were statistically significant in favor of ziprasidone from Day 7 until Day 21. For the OC analysis, the differences between mean change from baseline were not statistically significant for iloperidone at any time point.

Conclusions
The results of Study 3101 provide evidence that suggests efficacy of iloperidone at a dose of 24 mg/d, given twice daily, in the treatment of schizophrenia versus placebo over 28 days of treatment. Of note, the OC analysis was statistically significant in favor of ziprasidone compared to placebo for most time points, but for none of the time points for iloperidone.

Study B202

Because this study was a failed efficacy study, its efficacy results will not be described in detail.

Investigators/Sites
Eleven (11) investigators conducted this study at 11 sites in the U.S. Investigators and sites are listed in Appendix 10.3.21 in Section 10.3 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial was to evaluate the efficacy of 4 mg/d (2 mg b.i.d.) and 8 mg/d (4 mg b.i.d.) of HP873 (iloperidone) given for 42 days to schizophrenic patients in relieving the positive and negative symptoms of schizophrenia.

Patient Sample
Important inclusion criteria were:

- age 18 to 55 years

- male, surgically sterilized female
- had acute or relapsing schizophrenia according to DSM-III-R diagnostic criteria
- had hospital admission due to acute or relapsing schizophrenia, but no longer than 4 wks before the start of the placebo-washout period
- >/= 4 on at least 1 of 4 symptoms on the PANSS positive syndrome scale (delusions, conceptual disorganization, hallucinatory behavior, grandiosity)
- Rating at screening of moderate (4) or greater on the Clinical Global Impression (CGI) Severity of Mental Deterioration
- Ability to be maintained free of antipsychotics for a minimum of 4 days
- No requirement for any other routine psychotropic medication
- No requirement for a standard regimen of any other medication

The following were relevant exclusion criteria:

- Evidence of any chronic disease of the central nervous system
- Evidence of Substance Use Disorder (DSM-III-R) within the past 12 months or current illicit drug use
- Treatment with clozapine within 90 days of entry to the washout phase of the study
- Treatment with a depot neuroleptic within 1 treatment cycle before entry into the washout phase of the study
- Treatment within the previous 4 weeks of the washout phase with any drug known to have a well-defined potential for toxicity to a major organ (e.g., chloramphenicol)
- Treatment with an MAO inhibitor within 2 weeks before entry into the double-blind phase of the study
- Requirement for ECT or any routine psychotropic medication or other medication or other medication concomitantly
- Inability to abstain completely from alcohol during the study period

Design

This was a multicenter, double-blind, placebo-controlled study consisting of four phases: screening (Days -21 to -8), 7-day placebo washout (Days -7 to -1), 6-week double-blinded active treatment, and 1-week post-treatment follow-up. The washout period could be shortened to 4 days if a patient became too agitated or psychotic to tolerate a 7-day drug-free washout. After screening and washout, subjects were randomized to treatment (iloperidone or placebo) with a randomization schedule of 1:1:1. Subjects were given titrated doses of iloperidone from Day 1 through 10 of the active treatment phase. Subjects received a fixed dose of 2 mg bid and 4 mg bid until Day 42. Medication was stopped on Day 43.

Subjects were admitted to the treatment facility for screening, washout, and first 2 wks of double blind treatment. Patients could be discharged to a day hospital facility after Day 14 provided the following:

1. the patient was domiciled
2. the patient's clinical condition was compatible with outpatient treatment

3. no adverse events occurred or clinical condition existed which would put the patient at greater risk in an outpatient setting
4. the patient, in the judgment of the investigator, would return to the investigational site at weekly intervals for all scheduled safety, efficacy, and pharmacokinetic assessments
5. the patient, in the judgment of the investigator, would take the medication as prescribed
6. the patient, in the judgment of the investigator would attend the Day Hospital regularly

The following concomitant medications were permitted throughout the study:

1. chloral hydrate (up to 1500 mg/24 h) for insomnia or severe anxiety
2. acetaminophen (325 mg q 4 h prn) for pain
3. mylanta II (15 cc q 2 h prn) for gastric distress
4. colace (up to 200 mg/d prn) for constipation

Subjects received their medication twice daily during the double-blind treatment phase at 7 to 9 AM and 5 to 8 PM during or immediately following meals.

Dose titration in each dose group is described in the table below, extracted from the sponsor's submission.

	Dosing/Titration Schedule		
	Placebo	4 mg/day	8 mg/day
Days 1-2: *(1 capsule BID)*	1 placebo capsule BID	One 1-mg capsule BID	One 1-mg capsule BID
Total mg iloperidone /day	n/a	2 mg/day	2 mg/day
Days 3-5: *(2 capsules BID)*	2 placebo capsules BID	Two 1-mg capsules BID	Two 1-mg capsules BID
Total mg iloperidone /day	n/a	4 mg/day	4 mg/day
Days 6-9: *(3 capsules BID)*	3 placebo capsules BID	Two 1-mg capsules BID and 1 placebo capsule BID	Three 1-mg capsules BID
Total mg iloperidone /day	n/a	4 mg/day	6 mg/day
Days 10-14: *(1 capsule BID)*	1 placebo capsule BID	One 2-mg capsule BID	One 4-mg capsule BID
Total mg iloperidone /day	n/a	4 mg/day	8 mg/day
Days 15-42: *(1 capsule BID)*	1 placebo capsule BID	One 2-mg capsule BID	One 4-mg capsule BID
Total mg iloperidone /day	n/a	4 mg/day	8 mg/day

The PANSS was administered at screening, Day 1, Day 15, Day 22, Day 29, Day 36, and Day 43.

Efficacy Assessments

The protocol-defined primary efficacy variable was the Positive and Negative Syndrome Scale (PANSS) total score. No key secondary variables were identified.

Efficacy Analysis
The intent-to-treat (ITT) patients were those who:

- had a baseline evaluation performed
- at least one postbaseline evaluation was performed

The primary outcome measure was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at endpoint) within treatments and between treatments. General Linear Models (GLM) analyses were applied, using treatment and investigator as main effects. Investigator homogeneity (treatment-by-investigator interactions) was evaluated using treatment, investigator and treatment x investigator as the main effects.

Efficacy Results
Efficacy data displays may be found in the Appendix 10.3.22 in Section 10.3.

For the PANSS mean change from baseline analysis, the differences were not statistically significant.

Conclusions
The results of Study B202 do not provide adequate evidence of the efficacy of iloperidone in doses of 2 mg bid and 4 mg bid in the treatment of schizophrenia versus placebo over 42 days of treatment.

10.2 Line-by-Line Labeling Review

See section 9.4.

10.3 Appendix to Individual Study Reports

APPENDIX 10.3.1: LIST OF INVESTIGATORS FOR STUDY 3000

Site	Last Name	First Name	Affiliation	Address	City	State	ZIP
502	Daniel	David	Clinical Studies-Washington	6066 Leesburg Pike, 6th Floor	Falls Church	VA	22041
504	Ferguson	James	Pharmacology Research Clinic	448 East 6400 South, Suite 200	Salt Lake City	UT	84107
505	Hartford	James	Hartford Research Group	10550 Montgomery Road, Suite 20	Cincinnati	OH	45242
506	Iqbal	Naveed	Montefiore Medical Center	Department of Psychiatry, 111 East 210th Street, Klau Basement	Bronx	NY	10467
507	Lesem	Michael	Claghorn-Lesem Research Clinic	6750 West Loop South, Suite 1050	Bellaire	TX	77401
508	Litman	Robert	The Center for Behavioral Health Research	14915 Broschart Road, Suite 250	Rockville	MD	20850
509	Merideth	Charles	Affiliated Research Institute	8880 Rio San Diego Drive, Suite 1090	San Diego	CA	92108
510	Potkin	Steven	UCI Medical Center	101 The City Drive South	Orange	CA	92868
511	Rosenthal	Murray	Behavioral and Medical Research	3625 Ruffin Road, Suite 100	San Diego	CA	92123
518	Brown	David	Community Clinical Research	4411 Medical Parkway	Austin	TX	78756
519	Buckley	Peter	Case Western Reserve University, Department of Psychiatry	University Hospitals of Cleveland, 11100 Euclid Ave.	Cleveland	OH	44106
521	Chou	James	New York University Medical Center/ Bellevue Hospital Center	Department of Psychiatry, 462 First Avenue, Room 20W13A	New York	NY	10016
523	Miller Ereshefsky	Alexander Larry	Clinical Research Unit, San Antonio State Hospital	6711 S. New Braunfels	San Antonio	TX	78223
525	Reid (replaced Grissom) Grissom	Timothy Christine	Clinical Studies, Melbourne	1360 Sarno Road, Suite B	Melbourne	FL	32935
526	Hafez	Hisham	Foundation Medical Partners at Southern New Hampshire Health Systems, Institute for Clinical Research at the Medical Center	Ten Prospect Street	Nashua	NH	03060
527	Hamner	Mark	Ralph H. Johnson VA Medical Center, Psychiatry Service (116)	109 Bee Street	Charleston	SC	29401

Site	Last Name	First Name	Affiliation	Address	City	State	ZIP
529	Kang	Jasbir	Western Pennsylvania Psychiatric Center	150 Pleasant Drive, Suite G-5	Center Twp.	PA	15001
530	Kanof (satellite site was not distinguished by patient numbering)	Philip	VA Medical Center, Psychiatry Services (4-116A)	3601 S. Sixth Avenue	Tucson	AZ	85723
531	Bartzokis McClain	George Catina	VA Medical Center	2200 Fort Roots Drive, Building 170 Room 2N101 (116A-NLR)	North Little Rock	AR	72114
532	Kingsbury	Steven	Dallas VA North Texas Health Care System (116A)	4500 S. Lancaster Road	Dallas	TX	75216
533	Kolin	Irving	Orlando Regional Healthcare System	1065 West Morse Blvd., Suite 202	Winter Park	FL	32789
536	Riesenberg	Robert	Atlanta Center for Medical Research	625 Dekalb Industrial Way	Decatur	GA	30033
537	Reist	Christopher	VA Long Beach Healthcare System, Department of Mental Health 06/116A	5901 E. Seventh Street	Long Beach	CA	90822
538	Risch	Samuel	Medical University of South Carolina, Institute of Psychiatry, 502-North	67 President Street	Charleston	SC	29425
540	Shillcutt	Samuel	Department of Psychiatry and Behavioral Sciences, Mercer University School of Medicine	1508 College Street	Macon	GA	31207
541	Sokolski De Silva	Kenneth Himasiri	Affiliated Research Institute	801 N. Tustin Avenue, Suite 501	Santa Ana	CA	92705
543	Steinbook	Richard	University of Miami School of Medicine, Dept. of Psychiatry	1695 NW 9th Avenue, Room 2101	Miami	FL	33136
544	Tapp	Andre	VA Puget Sound Health Care System, Mental Health Service (116)	American Lake Division, Bldg 7A, Rm 129	Tacoma	WA	98493
545	Tran-Johnson	Tram	California Neuropsychopharmacology Clinical Research Institute	10737 Camino Ruiz, Suite 200	San Diego	CA	92126
546	Udelman	Harold	Biomedical Stress Research	45 East Osborn Road	Phoenix	AZ	85012
547	Vieweg	Victor	Hunter Holmes McGuire VA Medical Center	Psychiatry Service (116A) 1201 Broad Rock Boulevard	Richmond	VA	23249
548	Wassef	Adel	Harris County Psychiatry Center	2800 S. MacGregor Way	Houston	TX	77021

Site	Last Name	First Name	Affiliation	Address	City	State	ZIP
549	Wolkin	Adam	New York Department of Veteran Affairs Medical Center	423 East 23rd Street	New York	NY	10010
550	Preskorn	Sheldon	Psychiatric Research Institute	1100 North St. Francis, Suite 200	Wichita	KS	67214
551	Knesevich	Mary Ann	St. Paul Medical Center	5959 Harry Hines, Professional Building 1, Suite 924,	Dallas	TX	75235
552	Logue	H.E. (Harry)	Birmingham Psychiatry Pharmaceutical Studies	3490 Independence Drive	Birmingham	AL	35209
553	Davidson Solbach	Joyce M. Patricia	Menninger Clinic, Center for Clinical Research	5800 SW 6th Avenue	Topeka	KS	66606-9604
555	Janicak Winans	Philip Elizabeth	Psychiatric Institute	1601 W. Taylor	Chicago	IL	60612
556	Beckett (previously known by maiden name: Dabiri)	Louise	IPS Research	1211 North Shartel, Suite 407	Oklahoma City	OK	73103
558	Thomas	Marshall	Colorado Psychiatric Health, University North Pavilion	4455 E 12th Avenue	Denver	CO	80220
	Allen	Michael	Denver Health Medical Center	777 Bannock Street	Denver	CO	80204
559	Jaffe	Richard	Belmont Center for Comprehensive Treatment	4200 Monument Avenue	Philadelphia	PA	19131
560	Lowy	Adam	Psychiatric Institute of Washington, D.C.	4228 Wisconsin Avenue, NW	Washington	DC	20016
561	Townsend	Mark	LSU Medical Center in New Orleans Dept. of Psychiatry	1542 Tulane Ave.	New Orleans	LA	70112
562	West	Scott	Psychiatric Institute of Florida	77 West Underwood Street, 3rd floor	Orlando	FL	32806
563	Yoo	Tai P.	Mercy Hospital, Behavioral Medicine Services	5555 Conner Avenue	Detroit	MI	48213
564	Lindenmayer	Jean-Pierre	Nathan Kline Institute/Manhattan Psychiatric Center	Psychopharmacology Research Unit; Dunlap 14A; Ward's Island Complex	New York	NY	10035

APPENDIX 10.3.2: RESULTS OF PRIMARY VARIABLE PANSS: CHANGE FROM BASELINE, ALL TIME POINTS, LOCF ANALYSIS, ITT POPULATION FOR STUDY 3000

							P values for Pairwise Comparisons+				
Visit		Ilo 4 mg	Ilo 8 mg	Ilo 12 mg	Hal	Pbo	Ilo 4 mg vs Pbo	Ilo 8 mg vs Pbo	Ilo 12 mg vs Pbo	Hal vs Pbo	Ilo (8mg+12mg)/2 vs Pbo **
Week 1	N	113	114	115	114	117	0.710	0.928	0.646	0.120	0.751
	BSL Mean	95.0	95.7	94.6	96.1	95.0					
	BSL SD	15.3	15.9	14.8	15.6	17.0					
	Mean Change	2.3	2.7	3.8	5.8	3.0					
	Change SD	14.4	13.6	15.5	15.9	17.2					
	Adj. Change	3.1	4.0	4.7	6.8	3.8					
Week 2	N	113	114	115	114	117	0.936	0.335	0.387	<0.001*	0.291
	BSL Mean	95.0	95.7	94.6	96.1	95.0					
	BSL SD	15.3	15.9	14.8	15.6	17.0					
	Mean Change	3.6	5.4	5.4	11.1	3.5					
	Change SD	16.0	16.7	16.2	17.4	19.9					
	Adj. Change	4.3	6.2	6.0	12.1	4.1					
Week 3	N	113	114	115	114	117	0.259	0.238	0.098	<0.001*	0.102
	BSL Mean	95.0	95.7	94.6	96.1	95.0					
	BSL SD	15.3	15.9	14.8	15.6	17.0					
	Mean Change	5.6	5.5	7.0	11.1	3.4					
	Change SD	17.1	18.1	17.7	18.4	22.4					
	Adj. Change	6.9	7.1	8.2	12.7	4.3					

Week 4	N	113	114	115	114	117	0.124	0.277	0.015*	<0.001*	0.043*
	BSL Mean	95.0	95.7	94.6	96.1	95.0					
	BSL SD	15.3	15.9	14.8	15.6	17.0					
	Mean Change	6.5	5.1	8.7	12.0	3.1					
	Change SD	20.4	18.8	20.0	20.0	22.7					
	Adj. Change	7.8	6.7	10.0	13.5	3.9					
Week 5	N	113	114	115	114	117	0.146	0.466	0.065	<0.001*	0.137
	BSL Mean	95.0	95.7	94.6	96.1	95.0					
	BSL SD	15.3	15.9	14.8	15.6	17.0					
	Mean Change	7.3	5.2	8.2	11.9	4.1					
	Change SD	21.5	19.3	19.4	20.3	23.0					
	Adj. Change	8.5	6.6	9.5	13.3	4.8					
Week 6	N	113	114	115	114	117	0.097	0.227	0.047*	<0.001*	0.065
	BSL Mean	95.0	95.7	94.6	96.1	95.0					
	BSL SD	15.3	15.9	14.8	15.6	17.0					
	Mean Change	7.8	6.4	8.6	12.5	4.1					
	Change SD	22.2	20.2	19.6	21.3	24.1					
	Adj. Change	9.0	7.8	9.9	13.9	4.6					

Change is calculated as pre-post baseline value so that a positive change indicates improvement.
+ Based on t test using the ANCOVA model.
* p < 0.05 (two-tailed).
** Ilo (8mg+12mg)/2 is a treatment contrast to test the average of 8 mg group and 12 mg group versus placebo.
Adj. Change = Least squared mean change from the ANCOVA model.
Details of the analysis are found in the statistical appendix (Appendix 5.1).

APPENDIX 10.3.3: RESULTS OF PRIMARY VARIABLE PANSS: CHANGE FROM BASELINE, ALL TIME POINTS, OBSERVED-CASES ANALYSIS, ITT POPULATION FOR STUDY 3000

							P values for Pairwise Comparisons+				
Visit		Ilo 4 mg	Ilo 8 mg	Ilo 12 mg	Hal	Pbo	Ilo 4 mg vs Pbo	Ilo 8 mg vs Pbo	Ilo 12 mg vs Pbo	Hal vs Pbo	Ilo (8mg+12mg)/2 vs Pbo **
Week 1	N	113	113	115	114	117	0.694	0.968	0.694	0.190	0.803
	BSL Mean	95.0	95.7	94.6	96.1	95.0					
	BSL SD	15.3	16.0	14.8	15.6	17.0					
	Mean Change	2.6	3.0	4.0	5.6	3.4					
	Change SD	14.0	13.2	15.4	15.5	16.3					
	Adj. Change	3.5	4.3	5.0	6.7	4.2					
Week 2	N	97	93	96	86	91	0.634	0.397	0.369	<0.001*	0.316
	BSL Mean	94.9	94.5	94.8	96.3	95.2					
	BSL SD	15.0	16.1	14.6	14.8	15.9					
	Mean Change	5.1	8.5	8.1	15.2	5.9					
	Change SD	15.6	15.1	15.3	15.2	18.2					
	Adj. Change	5.3	8.3	8.4	15.4	6.4					
Week 3	N	87	79	81	76	72	0.949	0.438	0.154	0.005*	0.209
	BSL Mean	95.7	92.8	94.1	96.8	95.2					
	BSL SD	14.6	14.7	13.9	15.1	16.4					
	Mean Change	8.9	10.5	12.4	16.0	8.1					
	Change SD	15.4	16.5	16.0	16.2	20.7					
	Adj. Change	9.6	11.4	13.0	16.9	9.3					

Change is calculated as pre-post baseline value so that a positive change indicates improvement.
+ Based on t test using the ANCOVA model.
* p < 0.05 (two-tailed).
** Ilo (8mg+12mg)/2 is a treatment contrast to test the average of 8 mg group and 12 mg group versus placebo.
Adj. Change = Least squared mean change from the ANCOVA model.
Details of the analysis are found in the statistical appendix (Appendix 5.1).

Week 4	N	74	68	71	59	59	0.971	0.785	0.074	0.014*	0.242
	BSL Mean	95.6	92.2	93.4	95.5	95.5					
	BSL SD	14.9	15.4	14.1	14.0	17.0					
	Mean Change	12.2	11.9	16.1	19.9	10.8					
	Change SD	20.6	16.5	18.4	19.0	21.0					
	Adj. Change	11.7	12.7	16.9	19.3	11.7					
Week 5	N	56	51	56	49	45	0.594	0.780	0.864	0.381	0.797
	BSL Mean	95.3	90.8	94.7	94.6	94.2					
	BSL SD	14.6	15.5	14.7	15.0	16.1					
	Mean Change	17.1	15.8	18.7	21.8	17.9					
	Change SD	16.6	16.7	17.0	19.3	19.0					
	Adj. Change	17.3	17.9	18.1	21.3	18.7					
Week 6	N	51	44	50	42	39	0.904	0.181	0.914	0.071	0.476
	BSL Mean	96.1	90.3	94.0	94.4	94.4					
	BSL SD	14.6	15.9	14.5	15.2	16.5					
	Mean Change	19.9	19.8	20.2	23.6	17.8					
	Change SD	17.7	17.1	14.9	19.8	23.1					
	Adj. Change	19.4	23.4	18.4	25.0	18.5					

Change is calculated as pre-post baseline value so that a positive change indicates improvement.
+ Based on t test using the ANCOVA model.
* $p < 0.05$ (two-tailed).
** Ilo (8mg+12mg)/2 is a treatment contrast to test the average of 8 mg group and 12 mg group versus placebo.
Adj. Change = Least squared mean change from the ANCOVA model.
Details of the analysis are found in the statistical appendix (Appendix 5.1).

APPENDIX 10.3.4: RESULTS OF PRIMARY VARIABLE PANSS: CHANGE FROM BASELINE, WEEK 6, LOCF ANALYSIS, ITT POPULATION EXCLUDING SCHIZOAFFECTIVE PATIENTS, FOR STUDY 3000

	Ilo 4 mg	Ilo 8 mg	Ilo 12 mg	Ilo 8+12mg	Hal	Placebo
Sample size	83	78	82	160	70	78
LS Means*	9.2	4.8	10.1		12.9	3.5
Difference from placebo (95% CI)	5.7 (-0.5, 12.0)	1.4 (-4.9, 7.7)	6.7 (0.4, 13.0)	4.0 (-1.4, 9.5)	9.4 (2.9, 16.0)	
Unadjusted p-values	0.072	0.666	0.037	0.148	0.005	

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APPENDIX 10.3.5: LIST OF INVESTIGATORS FOR STUDY 3004

Site	Last name	First name	Affiliation	Address	City	State[1]	C[2]	ZIP
151	Hustig,	Harry	Glenside Hospital	226 Fullarton Road	Eastwood	SA	AUS	5063
152	Samuels,	Anthony	Palmerston Centre, Hornsby Ku-Ring-Gai Hospital	Level 2 Palmerston Road	Hornsby	NSW	AUS	2077
153	Muir,	Keith	Cairns Base Hospital	The Esplanade	Cairns	QLD	AUS	4870
154	Keks,	Nicholas	Alfred Hospital Department of Psychiatry and Research	Commercial Road Prahran Postal Address: C/-PO Box 315	Prahran	VIC	AUS	3181
161	Mertens,	Claudine	Psych. Klin. Sint-Camillus	Beukenlaan 20	Sint-Denijs-Westrem		B	9051
171	Azorin,	Jean-Michel	Chu Sainte-Marguertie	270, Bd De Sainte Marguerite, Bp 29	Marseille	Cedex 9	F	13274
172	Khidichian,	Frederic	Centre Hospitalier Specialise, Secteur 19	27 Rue Des 4eme Rg De Saphis Marocains, Bp 29	Rouffach		F	68250
173	Peretti,	Charles	Chu-Hopital Robert Debre, Service de Psychiatrie	Avenue du General Koenig	Reims	Cedex	F	51092
175	Zimmerman,	Marie-Agathe	CHU Hopital Civil Service du Pr Danion - Psychiatrie	1 Place de L'Hopital, Bp 426	Strasbourg		F	67091
176	Dassa,	Daniel	Hospital De La Timone, Service Du Pr Guidicelli	254, Rue Saint Pierre	Marseille	Cedex	F	13385
177	Chevrier,	Helene	Centre Hospitalier Specialise George Mazurelle, Service De Psychiatrie	Route De La Tranche	La Roche Sur Yon	Cedex	F	85026
178	Didi,	Roy	Chs De La Chartreuse, Service De Psychiatrie	1 Boulevard De Chanoine Kir, Bp 1514	Dijon	Cedex	F	21033
186	Balogh,	Akos	1st Department of Psychiatry, Ferenc Markhot Hospital of Heves County	Baktai ut 38	Budapest	Eger	H	3300
187	Furedi,	Janos	National Institute of Psychiatry and Neurology	Nyeki ut.10-21	Budapest		H	H-1021
188	Rihmer,	Zoltan	National Institute of Psychiatry and Neurology, Department of Psychiatry XIII.	Huvosvolgyi U. 116	Budapest		H	H-1021
189	Boldizsar,	Ferenc	Kaposi Mor County Hospital		Tallian Gy		H	U.20-34
190	Szabo,	Peter	Markusovszky Hospital Of Vas County, Department Of Psychiatry and Psychotherapy	11-es-Huszar	Tizenegyes		H	U.138
211	Brook,	Shlomo	Sterkfontein Hospital	Sterkfontein Road, Research Unit, Ward 8	Krugersdorp		ZA	1740
212	Hart,	George	Tara Hospital	50 Saxon Road	Hurlingham		ZA	2196

Site	Last name	First name	Affiliation	Address	City	State[1]	C[2]	ZIP
214	Rataemane, Solomon		Oranje Hospital, Research Unit	Victoria Road	Makgerbe	Bloemfontein	ZA	9300
216	Ramjee, Paresh		Vista Psychiatric Clinic	135 Gerhard Street	Centurion		ZA	0157
506	Lesem, Michael		Claghorn-Lesem Research Clinic, Inc.	6750 West Loop South, Suite 1050	Bellaire	TX	USA	77401
510	Potkin, Steve		UCI Medical Center	101 The City Drive South	Orange	CA	USA	92868
511	Rosenthal, Murray		Behavioral & Medical Research, LLC	3625 Ruffin Road, Suite 100	San Diego	CA	USA	92123
536	Riesenberg, Robert		Atlanta Center for Medical Research	625 Dekalb Industrial Way	Decatur	GA	USA	30033
545	Tran-Johnson, Tram		California Neuropsychopharmacology, Clinical Research Institute	10737 Camino Ruiz, Suite 230	San Diego	CA	USA	92126
559	Jaffe, Richard		Belmont Center for Comprehensive Treatment	4200 Monument Road	Philadelphia	PA	USA	19131
601	Ainslie, George		VA Medical Center, Coatesville, Psychiatry 38-116A	1400 Black Horse Hill Road	Coatesville	PA	USA	19320-2096
602	Bark, Nigel		Schizophrenic Research Unit Ward 19, Bronx Psychiatric Center	1500 Waters Place	Bronx	NY	USA	10461
603	Berry, Sally		Emory University School of Medicine, Department of Psychiatry	1707 Uppergate Drive, NE, Room 403	Atlanta	GA	USA	30322
604	Brenner, Ronald		Neurobehavioral Research, Inc.	144 Grove Ave.	Cedarhurst	NY	USA	11516
605	Crayton, John		Biologic Psychiatry Section 116A.7, Psychiatry Services 116A.7	Hines V.A. Hospital	Hines	IL	USA	60141
606	Dolgoff, Robert		Berkeley Therapy Institute	1749 Martin Luther King Jr. Way	Berkeley	CA	USA	94709
607	Grumet, Ross		Charter Behavioral Health System of Atlanta at Midtown, LLC	819 Juniper Street NE	Atlanta	GA	USA	30308
608	Halaris, Angelos		Dept of Psychiatry and Human Behavior, University Of Mississippi Medical Center	2500 North State Street	Jackson	MS	USA	39216-4505
609	Huey, Leighton		Department of Psychiatry, University of Connecticut Health Center	263 Farmington Ave.	Farmington	CT	USA	06030
611	Menza, Matthew		UMDNJ Robert Wood Johnson Medical School, Department Of Psychiatry	675 Hoes Lane-D321	Piscataway	NJ	USA	08854
612	Mofsen, Rick		Clinical Research Associates	3535 South Jefferson Avenue, Suite 304	St. Louis	MO	USA	63118

Site	Last name	First name	Affiliation	Address	City	State[1]	C[2]	ZIP
613	Pahl, Jorg		Pahl Brain Associates, P.C.	3909 N. Classen	Oklahoma City	OK	USA	73118
614	Parsa, Mahmoud		University Hospitals Health System	11100 Euclid Ave.	Cleveland	OH	USA	44160-5000
615	Ray, Derrell		Charter Anchor Behavioral Health System, LLC	5454 Yorktowne Drive	Atlanta	GA	USA	30349
616	Schooler, Nina		Hillside Hospital, Division of North Shore – Long Island Jewish Health System	Lowenstein Research Building, 266th Street & 76th Avenue	Glen Oaks	NY	USA	11004
617	Sinha, Dharm		Psychiatry Service (263), Uptown VA Medical Center	1 Freedom Way	Augusta	GA	USA	30904-6285
618	Small, Joyce		LaRue D. Carter Memorial Hospital	2601 Cold Spring Road	Indianapolis	IN	USA	46222-2202
619	Vivek, Seeth		Jamaica Hospital Medical Center - Department of Psychiatry	8900 Van Wyck Expressway	Jamaica	NY	USA	11418
620	Wirshing, Donna		VA Greater Los Angeles Healthcare System, Department of Psychiatry	11301 Wilshire Blvd., Building 210 Room 15 (B151H)	Los Angeles	NY	USA	90073
621	Figueroa, Carlos		3907 North Rosemead Road Boulevard, Suite 100		Rosemead	CA	USA	91770
622	Bari, Mohammed A.		Synergy Clinical Research Center	450 Fourth Avenue, Suite 409	Chula Vista	CA	USA	91910
623	Booker, J. Gary		GGS Psychiatric Clinic	827 Margaret Place, Suite 207	Shreveport	LA	USA	71101
624	Burgoyne, Karl		Harbour-UCLA Medical Center	1000 West Carson Street, Building F-9	Torrance	LA	USA	90502
627	Marks, Robert		Northwestern Medical Faculty Foundation, Dept. Of Psychiatry & Behavioral Science	675 North Saint Clair Street, Suite 20-250	Chicago	IL	USA	60611
628	Ginsberg, Lawrence		Red Oak Psychiatry Associates, PA	17115 Red Oak Drive, Suite 109	Houston	TX	USA	77090
629	Grossberg, George Habib, Asif (Habib replaced Grossberg)		St. Louis University School of Medicine, Department of Psychiatry, Wohl Memorial Institute	1221 South Grand Blvd.	St. Louis	MO	USA	63104
630	Johnson, Richard		VA Medical Center	1030 Jefferson Avenue, 116A	Memphis	TN	USA	38104-2193
631	Lauriello, John		University of New Mexico Health Sciences Center, Department of Psychiatry	2400 Tucker NE	Albuquerque	NM	USA	87131-5326
632	Lieberman, Jeffery		University of North Carolina School of Medicine, Department of Psychiatry	7025 Neurosciences Hospital Cb#760	Chapel Hill	NC	USA	27599-7160

Site	Last name	First name	Affiliation	Address	City	State[1]	C[2]	ZIP
633	McEvoy,	Joseph	John Umstead Hospital, Adult Admissions Unit	1003 12th Street Bldg 32	Butner	NC	USA	27509
636	Litman,	Robert	Centers for Behavioral Health	14915 Broschart Road, Suite 250	Rockville	MD	USA	20850
638	Smith,	Thomas	New York Presbyterian Hospital, Westchester Division	21 Bloomingdale Road	White Plains	NY	USA	10605
639	Ranjan,	Rakesh	Rakesh Ranjan and Associates	600 E. Smith Road Suite H	Medina	OH	USA	44256
640	Kwentus,	Joseph	Clinical Research Services at TCMC	600 Medical Park Drive, Suite 105	Madison	TN	USA	37115
641	Pigott,	Teresa	Comprehensive NeuroSciences, Inc.	4228 Wisconsin Avenue NW	Washington	DC	USA	20016
703	Labelle,	Alain	Royal Ottawa Hospital	Carmichael Bldg Room 1033C, 1145 Carling Avenue	Ottawa	ONT	CDN	K1Z 7K4
705	Reiss,	Jeffrey	PsycHealth - Health Science Center PZ202	771 Bannatyne Ave	Winnipeg	MB	CDN	R3E 3N4
706	Nandy,	Saibal		631 Prospect Drive SW	Medicine Hat	ALB	CDN	T1A 4C2

[1] Abbreviations for states and provinces are as follows: ALB = Alberta; CA = California; CT = Connecticut; DC = District of Columbia; GA = Georgia; IL = Illinois; IN = Indiana; LA = Louisiana; MB = Manitoba; MD = Maryland; MO = Missouri; MS = Mississippi; NC = North Carolina; NM = New Mexico; NSW = New South Wales; NY = New York; OH = Ohio; OK = Oklahoma; ONT = Ontario; PA = Pennsylvania; QLD = Queensland; SA = South Australia; TN = Tennessee; TX = Texas; Vic = Victoria.

[2] C = countries; abbreviations for countries are as follows: AUS = Australia; B = Belgium; CDN = Canada; F = France; H = Hungary; USA = United States; ZA = South Africa.

APPENDIX 10.3.6: RESULTS OF PRIMARY VARIABLE BPRS: CHANGE FROM BASELINE, ALL TIME POINTS, LOCF ANALYSIS, ITT POPULATION FOR STUDY 3004

						P values for Pairwise Comparisons+		
Visit		Ilo 4-8 mg	Ilo 10-16 mg	Ris	Pbo	Ilo 4-8 mg vs Pbo	Ilo 10-16 mg vs Pbo	Ris vs Pbo
Week 1	N	143	149	146	152	0.411	0.546	0.018*
	BSL Mean	54.9	54.1	54.7	54.2			
	BSL SD	8.8	9.1	10.0	9.8			
	Mean Change	3.9	3.4	5.7	2.8			
	Change SD	9.6	9.1	10.2	10.8			
	Adj. Change	3.7	3.5	5.4	2.8			
Week 2	N	143	149	146	152	0.529	0.232	0.001*
	BSL Mean	54.9	54.1	54.7	54.2			
	BSL SD	8.8	9.1	10.0	9.8			
	Mean Change	4.8	5.3	8.1	3.8			
	Change SD	10.0	10.4	12.4	12.2			
	Adj. Change	4.8	5.5	7.9	4.0			
Week 3	N	143	149	146	152	0.190	0.009*	<0.001*
	BSL Mean	54.9	54.1	54.7	54.2			
	BSL SD	8.8	9.1	10.0	9.8			
	Mean Change	5.1	6.5	9.0	2.9			
	Change SD	11.0	11.4	12.6	12.9			
	Adj. Change	4.8	6.4	8.8	3.0			

Week 4	N	143	149	146	152	0.050*	0.005*	<0.001*
	BSL Mean	54.9	54.1	54.7	54.2			
	BSL SD	8.8	9.1	10.0	9.8			
	Mean Change	6.1	6.8	10.7	2.8			
	Change SD	11.9	11.7	13.3	13.6			
	Adj. Change	5.6	6.7	10.1	2.8			
Week 5	N	143	149	146	152	0.005*	0.001*	<0.001*
	BSL Mean	54.9	54.1	54.7	54.2			
	BSL SD	8.8	9.1	10.0	9.8			
	Mean Change	6.5	7.0	10.9	2.2			
	Change SD	12.1	12.0	13.3	14.2			
	Adj. Change	6.1	6.7	10.2	2.1			
Week 6	N	143	149	146	152	0.012*	0.001*	<0.001*
	BSL Mean	54.9	54.1	54.7	54.2			
	BSL SD	8.8	9.1	10.0	9.8			
	Mean Change	6.7	7.6	11.1	2.7			
	Change SD	12.4	12.6	13.6	14.3			
	Adj. Change	6.2	7.2	10.3	2.5			

Change is calculated as pre-post baseline value so that a positive change indicates improvement.
+ Based on t test using the ANCOVA model.
* $p < 0.05$ (two-tailed).
Adj. Change = Least squared mean change from the ANCOVA model.
Details of the analysis are found in the statistical appendix (Appendix 5.1).

APPENDIX 10.3.7: RESULTS OF PRIMARY VARIABLE BPRS: CHANGE FROM BASELINE, ALL TIME POINTS, OC ANALYSIS, ITT POPULATION FOR STUDY 3004

						P values for Pairwise Comparisons+		
Visit		Ilo 4-8 mg	Ilo 10-16 mg	Ris	Pbo	Ilo 4-8 mg vs Pbo	Ilo 10-16 mg vs Pbo	Ris vs Pbo
Week 1	N	143	149	146	151	0.468	0.610	0.019*
	BSL Mean	54.9	54.1	54.7	54.2			
	BSL SD	8.8	9.1	10.0	9.8			
	Mean Change	3.9	3.5	5.8	3.0			
	Change SD	9.6	9.0	10.1	10.8			
	Adj. Change	3.8	3.5	5.6	3.0			
Week 2	N	124	127	123	129	0.824	0.148	0.006*
	BSL Mean	54.9	53.7	55.2	54.4			
	BSL SD	9.1	8.8	10.2	9.3			
	Mean Change	5.7	6.7	9.2	5.1			
	Change SD	10.0	9.9	12.2	12.1			
	Adj. Change	5.8	7.3	9.0	5.5			
Week 3	N	106	119	115	108	0.294	0.014*	0.002*
	BSL Mean	55.3	53.8	55.6	54.1			
	BSL SD	9.0	8.5	10.2	9.3			
	Mean Change	7.5	8.9	10.3	5.7			
	Change SD	10.8	10.9	11.9	12.5			
	Adj. Change	7.4	9.3	10.4	5.9			

Week 4	N	98	112	105	92	0.140	0.014*	<0.001*
	BSL Mean	55.3	53.6	55.8	54.0			
	BSL SD	9.2	8.4	10.1	9.1			
	Mean Change	9.4	9.9	12.5	6.6			
	Change SD	11.7	10.7	12.3	13.2			
	Adj. Change	8.8	10.3	12.1	6.4			
Week 5	N	80	93	91	64	0.134	0.055	0.004*
	BSL Mean	55.4	53.8	55.8	53.0			
	BSL SD	9.2	8.4	10.3	7.9			
	Mean Change	11.3	11.1	13.8	8.6			
	Change SD	11.0	10.5	11.7	13.1			
	Adj. Change	12.1	12.6	14.3	9.5			
Week 6	N	74	87	88	60	0.477	0.050	0.030*
	BSL Mean	54.4	53.6	55.7	53.3			
	BSL SD	8.8	8.3	10.3	8.3			
	Mean Change	11.7	12.9	15.1	10.9			
	Change SD	11.3	10.9	12.4	12.6			
	Adj. Change	12.6	14.7	15.0	11.4			

Change is calculated as pre-post baseline value so that a positive change indicates improvement.
+ Based on t test using the ANCOVA model.
* $p < 0.05$ (two-tailed).
Adj. Change = Least squared mean change from the ANCOVA model.
Details of the analysis are found in the statistical appendix (Appendix 5.1).

APPENDIX 10.3.8: RESULTS OF PRIMARY VARIABLE BPRS: CHANGE FROM BASELINE, ENDPOINT, LOCF ANALYSIS, ITT POPULATION EXCLUDING SCHIZOAFFECTIVE PATIENTS, FOR STUDY 3004

	Ilo 4-8 mg	Ilo 10-16 mg	Risp	Placebo
Sample size	115	121	110	116
LS Means *	5.77	6.51	10.31	4.86
Difference from placebo	0.91	1.66	5.46	
(95% confidence interval)	(-2.33, 4.16)	(-1.52, 4.83)	(2.23, 8.69)	
Unadjusted p-values	0.581	0.306	0.001	

APPENDIX 10.3.9: RESULTS OF PRIMARY VARIABLE BPRS: CHANGE FROM BASELINE, ALL TIME POINTS, LOCF ANALYSIS, ITT POPULATION EXCLUDING SCHIZOAFFECTIVE PATIENTS, FOR STUDY 3004

	Ilo 4-8mg	Ilo 10-16mg	Risp	Pbo	Ilo 4-8mg – Pbo		Ilo 10-16mg – Pbo		Risp – Pbo	
					Diff	p-value*	Diff	p-value*	Diff	p-value*
Week 1	3.73	3.28	5.94	3.15	0.59	0.634	0.13	0.914	2.79	0.023
Week 2	4.09	4.76	8.01	5.12	-1.03	0.456	-0.36	0.787	2.88	0.036
Week 3	4.20	5.84	8.51	4.78	-0.59	0.702	1.05	0.483	3.72	0.015
Week 4	5.53	6.10	9.93	4.63	0.90	0.572	1.47	0.347	5.30	0.001
Week 5	5.80	6.13	10.10	4.42	1.38	0.394	1.71	0.279	5.68	0.001
Week 6	5.77	6.51	10.31	4.86	0.91	0.581	1.66	0.306	5.46	0.001

* p-values are not adjusted for multiple comparisons

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APPENDIX 10.3.11: RESULTS OF PRIMARY VARIABLE BPRS: CHANGE FROM BASELINE, ALL TIME POINTS, LOCF ANALYSIS, ITT POPULATION INCLUDING SCHIZOAFFECTIVE PATIENTS, FOR STUDY 3005

Treatment group	Ilo 12-16 mg/d (N=230)	Ilo 20-24 mg/d (N=141)	Ris (N=148)	Pbo (N=152)
Baseline	54.4	54.9	55.0	55.4
Week 1	2.6	3.2	4.9*	2.8
Week 2	4.9	5.5	8.4*	4.0
Week 3	6.9*	6.7*	9.8*	4.1
Week 4	7.5*	8.1*	10.9*	5.1
Week 5	7.7*	8.6*	11.6*	5.2
Week 6	7.1	8.6*	11.5*	5.0

N=number of patients; Ilo=iloperidone; Ris=risperidone; Pbo=placebo; BPRS=18-item Brief Psychiatric Rating Scale score

* P<0.05 (two-tailed) compared with placebo; based on t-test using ANCOVA model.

Note: Change is calculated as a pre-post baseline value, so that a positive change indicates improvement and a negative change reflects worsening on the scale. Adjusted change = Least squared mean change from the ANCOVA model (including treatment, center, baseline and the treatment-by-baseline).

Source: Post-text Table 9.1-2

APPENDIX 10.3.12: RESULTS OF PRIMARY VARIABLE BPRS: CHANGE FROM BASELINE, ALL TIME POINTS, OC ANALYSIS, ITT POPULATION INCLUDING SCHIZOAFFECTIVE PATIENTS, FOR STUDY 3005

						P values for Pairwise Comparisons+		
Visit		Ilo 12-16 mg	Ilo 20-24 mg	Ris	Pbo	Ilo 12-16 mg vs Pbo	Ilo 20-24 mg vs Pbo	Ris vs Pbo
Week 1	N	230	141	148	152	0.675	0.882	0.020*
	BSL Mean	54.4	54.9	55.0	55.4			
	BSL SD	7.3	8.0	8.8	8.2			
	Mean Change	3.0	3.4	5.3	3.3			
	Change SD	8.0	6.5	6.9	8.2			
	Adj. Change	2.7	3.1	4.9	3.0			
Week 2	N	191	118	140	129	0.220	0.181	0.004*
	BSL Mean	54.2	54.7	54.9	55.2			
	BSL SD	7.4	7.7	9.0	8.3			
	Mean Change	6.8	7.1	8.9	5.9			
	Change SD	9.4	9.0	8.5	9.4			
	Adj. Change	6.7	7.0	8.6	5.5			
Week 3	N	166	105	129	112	<0.001*	0.017*	<0.001*
	BSL Mean	54.3	54.8	54.8	55.4			
	BSL SD	7.3	7.8	9.0	8.6			
	Mean Change	10.4	8.9	10.9	6.3			
	Change SD	10.1	8.7	9.5	11.4			
	Adj. Change	11.0	9.8	10.9	6.7			

Week 4	N	148	91	123	100	0.006*	0.014*	0.002*
	BSL Mean	54.2	54.9	54.3	54.7			
	BSL SD	7.2	7.9	8.1	8.6			
	Mean Change	12.2	11.7	13.5	9.4			
	Change SD	10.2	9.4	9.1	11.4			
	Adj. Change	12.6	12.7	13.3	9.3			
Week 5	N	134	91	116	92	0.012*	0.025*	0.003*
	BSL Mean	54.5	54.9	54.1	54.4			
	BSL SD	7.0	7.9	8.3	8.1			
	Mean Change	13.8	12.8	15.0	10.6			
	Change SD	10.3	9.7	8.7	12.5			
	Adj. Change	14.0	13.9	14.7	10.7			
Week 6	N	131	86	112	84	0.071	0.059	0.004*
	BSL Mean	54.3	55.0	53.9	54.2			
	BSL SD	7.2	7.7	8.1	7.8			
	Mean Change	13.0	12.9	14.9	10.3			
	Change SD	11.5	11.4	9.6	12.3			
	Adj. Change	13.1	13.6	14.9	10.5			

Change is calculated as pre-post baseline value so that a positive change indicates improvement.
+ Based on t test using the ANCOVA model.
* $p < 0.05$ (two-tailed).
Adj. Change = Least squared mean change from the ANCOVA model.
Details of the analysis are found in the statistical appendix (Appendix 5.1).

APPENDIX 10.3.13: RESULTS OF PRIMARY VARIABLE BPRS: CHANGE FROM BASELINE, ENDPOINT, LOCF ANALYSIS, ITT POPULATION EXCLUDING SCHIZOAFFECTIVE PATIENTS, FOR STUDY 3005

BPRS	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Pbo
Sample size	178	111	119	113
LS Means*	7.4	8.8	11.4	4.3
Difference from placebo (95% CI)	3.1 (0.3, 5.9)	4.5 (1.3, 7.6)	7.1 (4.0,10.2)	
Unadjusted p-values Risp as a reference	0.033 0.005	0.005 0.093	<0.001	<0.001

APPENDIX 10.3.14: RESULTS OF PRIMARY VARIABLE BPRS: CHANGE FROM BASELINE, ALL TIME POINTS, LOCF ANALYSIS, ITT POPULATION EXCLUDING SCHIZOAFFECTIVE PATIENTS, FOR STUDY 3005

	Ilo 12-16mg	Ilo 20-24mg	Risp 6-8mg	Pbo	Ilo 12-16mg - Pbo		Ilo 20-24mg - Pbo		Risp - Pbo	
					Diff	p-value*	Diff	p-value*	Diff	p-value*
Week 1	2.5	3.1	5.0	3.0	-0.5	0.614	0.2	0.862	2.1	0.033
Week 2	4.7	5.5	8.8	4.1	0.7	0.559	1.4	0.247	4.7	<0.001
Week 3	6.9	6.9	10.0	3.9	3.0	0.022	3.1	0.034	6.1	<0.001
Week 4	7.7	7.9	11.1	4.8	2.9	0.033	3.2	0.037	6.3	<0.001
Week 5	7.8	8.9	11.7	4.8	3.0	0.038	4.1	0.010	6.9	<0.001
Week 6	7.4	8.8	11.4	4.3	3.1	0.033	4.5	0.005	7.1	<0.001

* p-values are not adjusted for multiple comparisons

APPENDIX 10.3.15: RESULTS OF PRIMARY VARIABLE BPRS: CHANGE FROM BASELINE, ENDPOINT, OC ANALYSIS, ITT POPULATION EXCLUDING SCHIZOAFFECTIVE PATIENTS, FOR STUDY 3005

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Sample size	102	72	92	60
LS Means *	13.9	13.5	14.4	9.3
Difference from placebo	4.6	4.2	5.1	
(95% confidence interval)	(1.3, 7.9)	(0.7, 7.8)	(1.7, 8.4)	
Unadjusted p-values	0.006	0.019	0.003	

APPENDIX 10.3.16: RESULTS OF PRIMARY VARIABLE BPRS: CHANGE FROM BASELINE, ENDPOINT, LOCF ANALYSIS, ITT POPULATION EXCLUDING SCHIZOAFFECTIVE PATIENTS, FOR STUDY 3005; PRE- VERSUS POST-DOSE MODIFICATION

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Pre-dose modification				
Sample size	68	NA	38	39
LS Means *	5.14		10.60	4.60
Difference from placebo	0.54		6.00	
(95% confidence interval)	(-5.20, 6.28)		(-0.35, 12.35)	
Unadjusted p-values	0.851		0.064	
Post-dose modification				
Sample size	110	111	81	74
LS Means *	8.05	9.27	11.32	4.43
Difference from placebo	3.63	4.84	6.90	
(95% confidence interval)	(0.02, 7.23)	(1.28, 8.41)	(3.07, 10.73)	
Unadjusted p-values	0.049	0.008	<0.001	

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APPENDIX 10.3.18: PANSS TOTAL SCORE: ADJUSTED MEAN CHANGE (STANDARD ERROR) FROM BASELINE, STUDY 3101 (MMRM ANALYSIS, MITT POPULATION)

	Iloperidone 24 mg/d (N=283)	**Ziprasidone 160 mg/d (N=144)**	**Placebo (N=140)**
Baseline	92.88	90.95	90.48
Day 7	–4.29 (0.62)	–6.56 (0.87)	–4.22 (0.89)
Day 10	–7.01 (0.72)	–8.60 (1.01)[a]	–5.16 (1.03)
Day 14	–8.65 (0.86)	–10.02 (1.20)[a]	–5.85 (1.23)
Day 21	–10.56 (0.93)[a,b]	–11.54 (1.31)[a]	–6.84 (1.34)
Day 28	–12.01 (1.03)[c,d]	–12.27 (1.44)[a]	–7.08 (1.48)

MMRM = mixed-model repeated measures; ITT = intent-to-treat; PANSS-T = Positive and Negative Syndrome Scale total score.

[a] $P < 0.05$ (2-tailed) compared with placebo based on MMRM analysis using baseline as covariate.

[b] $P < 0.05$ (2-tailed) compared with placebo based on MMRM analysis using the randomization test method (1000 iterations). The randomization test method was only applied to the iloperidone vs. placebo comparison.

[c] $P < 0.01$ (2-tailed) compared with placebo based on MMRM analysis using baseline as covariate.

[d] $P < 0.01$ (2-tailed) compared with placebo based on MMRM analysis using the randomization test method (1000 iterations).

Source: Post-text Table 9.2.1-2a.

APPENDIX 10.3.19: PANSS TOTAL SCORE CHANGE FROM BASELINE TO DAY 28, STUDY 3101 (OC ANALYSIS, MITT POPULATION)

Visit		Ilo N = 283	Zip N = 144	Pbo N = 140	Pairwise Mean Differences		
					Ilo vs Pbo	Zip vs Pbo	Ilo vs Zip
Day 7 (Week 1)	n	281	142	139			
	BSL Mean	92.96	91.07	90.42			
	BSL SD	13.13	11.47	12.25			
	Mean Change	-4.20	-6.52	-3.98			
	Change SD	9.45	13.21	9.82			
	Adj. Change	-4.27	-6.65	-4.11	-0.16	-2.54	2.38
	Adj. Change (SE)	0.62	0.87	0.89	1.09	1.24	1.08
	95% C.I.	-5.49, -3.06	-8.37, -4.94	-5.86, -2.36	-2.30, 1.98	-4.98, -0.10	0.26, 4.49
	p-value ++				0.882	0.041*	0.028*
Day 10	n	254	131	125			
	BSL Mean	92.75	90.44	89.98			
	BSL SD	13.40	11.46	10.97			
	Mean Change	-7.86	-9.55	-6.42			
	Change SD	11.33	13.68	11.06			
	Adj. Change	-7.52	-9.68	-6.15	-1.78	-3.74	1.96
	Adj. Change (SE)	0.73	1.02	1.06	1.30	1.46	1.26
	95% C.I.	-9.36, -6.49	-11.65, -7.88	-8.23, -4.06	-4.33, 0.77	-6.61, -0.87	-0.52, 4.44
	p-value +				0.166	0.009**	0.109
	Interaction Adj BSL-by-Treatment = 0.056 @						
	Adj BSL 25th Percentile	-6.38	-6.36	-5.42	0.550	0.605	0.988
	Adj BSL 50th Percentile	-7.68	-9.33	-6.06	0.204	0.023*	0.195
	Adj BSL 75th Percentile	-9.15	-12.68	-6.72	0.227	0.001**	0.018*

Day 14 (Week 2)	n	238	123	118			
	BSL Mean	92.21	90.40	89.48			
	BSL SD	12.82	11.44	10.56			
	Mean Change	-9.79	-11.15	-7.31			
	Change SD	12.66	16.10	14.51			
	Adj. Change	-9.59	-11.62	-7.21	-2.79	-4.42	1.63
	Adj. Change (SE)	0.87	1.21	1.27	1.54	1.74	1.50
	95% C.I.	-11.71, -5.28	-14.01, -9.24	-9.70, -4.72	-5.82, 0.24	-7.84, -0.99	-1.32, 4.58
	p-value +				0.067	0.008**	0.232
	Interaction Adj BSL-by-Treatment = 0.095 @						
	Adj BSL 25th Percentile	-7.62	-7.10	-5.62	0.251	0.489	0.787
	Adj BSL 50th Percentile	-9.71	-11.09	-7.02	0.030	0.019*	0.363
	Adj BSL 75th Percentile	-11.80	-15.07	-8.42	0.071	0.002**	0.061
Day 21 (Week 3)	n	220	106	105			
	BSL Mean	92.20	91.00	89.34			
	BSL SD	12.61	11.80	10.34			
	Mean Change	-12.07	-14.31	-9.67			
	Change SD	13.67	16.22	15.46			
	Adj. Change	-12.25	-14.81	-10.15	-2.11	-4.66	2.55
	Adj. Change (SE)	0.94	1.35	1.38	1.69	1.92	1.65
	95% C.I.	-14.10, -10.40	-17.46, -12.15	-12.86, -7.43	-5.42, 1.20	-8.43, -0.89	-0.69, 5.79
	p-value ++				0.212	0.016*	0.123

Day 28 (Week 4)	n	200	102	93			
	BSL Mean	91.90	90.63	89.67			
	BSL SD	12.52	11.96	10.62			
	Mean Change	-14.92	-15.52	-12.04			
	Change SD	13.96	17.08	15.68			
	Adj. Change	-14.59	-16.44	-12.84	-1.75	-3.60	1.84
	Adj. Change (SE)	0.99	1.40	1.49	1.81	2.04	1.72
	95% C.I.	-16.55, -12.64	-19.18, -13.65	-15.78, -9.90	-5.32, 1.81	-7.60, 0.41	-1.55, 5.23
	p-value ++				0.334	0.075	0.286

\+ p-value from an ANCOVA model including 'Adjusted Baseline', 'Treatment (Ilo, Zip, Pbo)', 'Pooled-Center' and the interaction 'Adjusted Baseline-by-Treatment'.

++ p-value from an ANCOVA model including 'Adjusted Baseline', 'Treatment (Ilo, Zip, Pbo)' and 'Pooled-Center'. The interaction 'Adjusted Baseline-by-Treatment' was not found significant at the 0.10 alpha level and was thus removed from the model.

§ The interaction 'Adjusted Baseline-by-Treatment' was found significant at the 0.10 level from the ANCOVA model. Therefore, the Adj. Change for each treatment and the pairwise p-values were presented under each proposed adjusted baseline percentile.

* p-value < 0.05; ** p-value < 0.01 (2 tailed)

Notes:

1. The Baseline is defined as the last non-missing evaluation preceding the first dose of study medication. Included in the baseline summaries are patients with both a Baseline and post-baseline values.
2. Change is calculated as post-pre baseline value so that a negative change indicates improvement.
3. Adj. Baseline = Timepoint Baseline Value - Mean of Overall Baseline Values.
4. Adj. Change = Least squared mean change from the ANCOVA model.
5. Details of the analysis are found in the statistical appendix (Appendix 5.1).

APPENDIX 10.3.20: PANSS TOTAL SCORE: ADJUSTED MEAN CHANGE (STANDARD ERROR) FROM BASELINE FOR CNTF (-) PATIENTS, STUDY 3101 (MMRM ANALYSIS, MITT POPULATION)

Time point	Iloperidone *CNTF (-)* 24 mg/d (N=218)	Placebo *CNTF (-)* (N=107)
Day 7	–4.16 (0.71)	–3.40 (1.02)
Day 10	–7.31 (0.83)[a]	–4.37 (1.18)
Day 14	–8.61 (0.98)[a]	–5.04 (1.40)
Day 21	–10.27 (1.07)[a]	–6.28 (1.54)
Day 28	–12.05 (1.17)[b]	–5.68 (1.69)

PANSS-T = Positive and Negative Syndrome Scale total score; MMRM = Mixed Model Repeated Measures; ITT = intent-to-treat.
[a] $P < 0.05$ (2-tailed) compared with placebo based on MMRM analysis with baseline as covariate.
[b] $P < 0.01$ (2-tailed) compared with placebo based on MMRM analysis with baseline as covariate.
Source: Post-text Table 9.2.1-2b.

APPENDIX 10.3.21: LIST OF INVESTIGATORS FOR STUDY B202

INV NO.	NAME/LOCATION
006	Richard L. Borison, MD, PhD. Department of Psychiatry & Health Behavior Medical College of Georgia 1515 Pope Avenue Augusta, GA 30912-3800 (404) 721-3284
007	Jose M. Canive, M.D. Veterans Affairs Medical Center 2100 Ridgecrest Drive, S.E. Albuquerque, NM 87108
008	Dwight Evans, M.D. Department of Psychiatry University of Florida P.O. Box 100256 1600 SW Archer Road Gainesville, FL 32610-0256 (904) 392-3681
009	Louis F. Fabre, M.D., Ph.D. 5503 Crawford Houston, TX 77004
010	Lawrence E. Adler, M.D. Associate Professor of Psychiatry Box C268-16, Psychiatry University of Colorado Health Sciences Center 4200 E. 9th Avenue Denver, CO 80262 Robert Freedman, M.D. Professor of Psychiatry & Pharmacology Box C268-71, Psychiatry University of Colorado Health Science Center 4200 E. 9th Avenue Denver, CO 80262
011	Craig N. Karson, M.D. VA Medical Center 2200 Fort Roots Drive North Little Rock, AR 72114

012	Charles B. Nemeroff, M.D., Ph.D. Department of Psychiatry & Behavioral Sciences Emory University School of Medicine 1639 Pierce Drive, Suite 4000, Drawer AF Atlanta, GA 30322-4990
013	Murray H. Rosenthal, D.O. 9449 Balboa Boulevard Suite 205 San Diego, CA 92123
014	Mary E. Swigar Robert Wood Johnson Medical - UMDNJ 1 Robert Wood Johnson Place New Brunswick, NJ 08903
015	Allan Douglass, M.D. Psychiatry 116-A Ann Arbor VA 2215 Fuller Road Ann Arbor, MI 48105
016	Eduardo Val, M.D./018 Department of Psychiatry (0655) UCSD School of Medicine 9500 Gilman Drive La Jolla, Ca 92093

APPENDIX 10.3.22: PANSS TOTAL SCORE, MEAN CHANGE FROM BASELINE IN WEEKLY SCORES FOR STUDY B202, LOCF ANALYSIS, ITT POPULATION

	Placebo			Iloperidone (2 mg BID)				Iloperidone (4 mg BID)			
Visit	N	Mean Chg[1]	P-Value[2]	N	Mean Chg[1]	P-Value[2]	P value[3]	N	Mean Chg[1]	P-Value[2]	P value[3]
Baseline	31			32				28			
Day 8	5	4.00	0.659	6	8.50	0.258	0.748	4	-21.3	0.185	0.083
Day 15	29	-6.97	0.034	29	-3.03	0.413	0.380	25	-10.3	0.001	0.388
Day 22	23	-9.65	0.012	26	-7.19	0.015	0.311	21	-12.5	0.002	0.906
Day 29	21	-9.62	0.069	24	-12.9	<0.001	0.873	16	-17.5	0.002	0.246
Day 36	18	-14.3	0.022	22	-14.2	<0.001	0.570	16	-22.5	0.001	0.337
Day 43	17	-18.4	0.010	22	-12.1	0.003	0.243	15	-26.8	<0.001	0.429
EP[4]	31	-6.68	0.146	32	-4.13	0.275	0.521	28	-18.2	<0.001	0.077

[1] Mean Chg. = means change from baseline
[2] P-value = Within treatment Groups
[3] P-Value = Between Treatment Groups (placebo and 2 mg BID or 4 mg BID)
[4] EP = Last Observation Carried Forward
Baseline Mean Scores: Placebo = 97.71, Iloperidone (2 mg) BID = 90.56, Iloperidone (4 mg bid)= 100.5

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10.4 Appendix to Data Sources, Review Strategy, and Data Integrity (Section 4)

APPENDIX 10.4.1: CLINICAL INVESTIGATORS WITH UNOBTAINABLE FINANCIAL DISCLOSURE INFORMATION

Study ILP3005
Site 502
Forster, David J.
Prochnik, Elizabeth
Site 509
Watson, Marian
Site 511
Corbett, Kimberly
Sterlieb, Geoffrey
Site 544
Purcell, Heather
Site 545
Azar-Cavanagh, Madelynn
Benbow, Christopher
Lorenz, Martin
Sinno, Bassam
Site 559
Young, Vincent
Site 564
Chowdhury, Quamrul
Hay, Shelly
Everett, Monica
Site 629
Davitt, Bradley
Site 851
Worrell, Toni
Site 852

Ohemeng, Kwame
Prince, Andrew
Prince, Sabrina
Site 853
Arnold, Julia
Site 858
Patel, Jayendra
Schlossman, Deborah
Singh, Jaskaran
Site 860
Ertugrul, Aygun
Han, Jihyuk
Humphrey, Traci
Site 865
Jackson, Amy
Site 921
Habibond, Fadie
Lavic-Kosic, Gordana
Pavicic, Matija
Smrkinic, Tamara
Zwingl, Anne
Site 924
Butoric, Jadranba
Marcinko, Darko
Mauracic, Minike
Petritek, Igor
Site 925
Kunovic, Ninoslav
Solenicki, Gordana
Todoric, Ivan
Visiya, Sucevie
Site 943
Leucht
Site 948
Bela, Raolnai
Krisltics, Anna
Tamas, Halda
Site 961
GovBychov, Alona
Levy, Aya
Piziatinsky, Boris
Simonov, Inne
Site 962
Assael-Awir, Miriam
Avital, Levin
Drew-Apoteker, P. Nina
Kofman, Nily
Site 964

Bassat-Harrar, Pazit
Kurs, Rena
Landau, Moshe
Piriatinsky, Boris
Site 971
Bialaczewski A.
Gascon, Rupinto
Kaczorowska, Iwona
Sabela-Koska, Ewa
Site 975
Augusiyniah, Ewa
Kasperswa-Sobczyv, Yolania
Sustowski, Pawet
Site 976
Dobrowolski, M.
Grezicka, E.
Site 983
Grobler, D.
Price, S.

10.5 Appendix to Integrated Review of Safety (Section 7)

APPENDIX 10.5.1: SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS BY BODY SYSTEM BY TREATMENT

SOC/ Preferred Term	Placebo (N=672)	Iloperidone 0.5-4 mg/day (N=352)	Iloperidone 4-8 mg/day (N=1488)	Iloperidone 10-16 mg/day (N=1621)	Iloperidone 20-24 mg/day (N=617)	Iloperidone Combined (N=4078)
Patients With at Least One Serious TEAE	49 (7.3%)	7 (2.0%)	235 (15.8%)	363 (22.4%)	37 (6.0%)	642 (15.7%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**0**	**0**	**1 (0.1%)**	**3 (0.2%)**	**0**	**4 (0.1%)**
ANAEMIA	0	0	0	1 (0.1%)	0	1 (0.0%)
GRANULOCYTOPENIA	0	0	0	1 (0.1%)	0	1 (0.0%)
LEUKOPENIA	0	0	1 (0.1%)	0	0	1 (0.0%)
MICROCYTIC ANAEMIA	0	0	0	1 (0.1%)	0	1 (0.0%)
CARDIAC DISORDERS	**4 (0.6%)**	**0**	**8 (0.5%)**	**9 (0.6%)**	**0**	**17 (0.4%)**
TACHYCARDIA	0	0	1 (0.1%)	2 (0.1%)	0	3 (0.1%)
CARDIAC FAILURE CONGESTIVE	0	0	1 (0.1%)	1 (0.1%)	0	2 (0.1%)
MYOCARDIAL INFARCTION	2 (0.3%)	0	0	2 (0.1%)	0	2 (0.1%)
PALPITATIONS	0	0	1 (0.1%)	1 (0.1%)	0	2 (0.1%)
ARRHYTHMIA	0	0	1 (0.1%)	0	0	1 (0.0%)
CARDIAC ARREST	0	0	1 (0.1%)	0	0	1 (0.0%)
CARDIAC FAILURE	0	0	1 (0.1%)	0	0	1 (0.0%)
CARDIO-RESPIRATORY ARREST	0	0	0	1 (0.1%)	0	1 (0.0%)
CORONARY ARTERY DISEASE	0	0	0	1 (0.1%)	0	1 (0.0%)

SINUS ARRHYTHMIA	0	0	0	1 (0.1%)	0	1 (0.0%)
SUPRAVENTRICULAR TACHYCARDIA	0	0	1 (0.1%)	0	0	1 (0.0%)
VENTRICULAR EXTRASYSTOLES	0	0	1 (0.1%)	0	0	1 (0.0%)
ANGINA PECTORIS	1 (0.1%)	0	0	0	0	0
BRADYCARDIA	1 (0.1%)	0	0	0	0	0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0	1 (0.1%)	0	0	1 (0.0%)
HYDROCELE	0	0	1 (0.1%)	0	0	1 (0.0%)
EAR AND LABYRINTH DISORDERS	0	1 (0.3%)	0	0	0	1 (0.0%)
TINNITUS	0	1 (0.3%)	0	0	0	1 (0.0%)
TYMPANIC MEMBRANE PERFORATION	0	0	0	0	0	0
ENDOCRINE DISORDERS	0	0	0	1 (0.1%)	0	1 (0.0%)
GOITRE	0	0	0	1 (0.1%)	0	1 (0.0%)
EYE DISORDERS	0	0	1 (0.1%)	0	0	1 (0.0%)
MACULAR DEGENERATION	0	0	1 (0.1%)	0	0	1 (0.0%)
MYOPIA	0	0	0	0	0	0
OCULOGYRATION	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	2 (0.3%)	0	5 (0.3%)	9 (0.6%)	3 (0.5%)	17 (0.4%)
DIARRHOEA	0	0	1 (0.1%)	2 (0.1%)	0	3 (0.1%)
ABDOMINAL DISCOMFORT	0	0	0	2 (0.1%)	0	2 (0.0%)
INGUINAL HERNIA	0	0	1 (0.1%)	0	1 (0.2%)	2 (0.0%)
NAUSEA	0	0	1 (0.1%)	1 (0.1%)	0	2 (0.0%)
ABDOMINAL ADHESIONS	0	0	0	1 (0.1%)	0	1 (0.0%)
ABDOMINAL PAIN	0	0	0	1 (0.1%)	0	1 (0.0%)
DUODENAL ULCER	0	0	0	1 (0.1%)	0	1 (0.0%)
GASTRIC ULCER	0	0	0	1 (0.1%)	0	1 (0.0%)
GASTRITIS	0	0	1 (0.1%)	0	0	1 (0.0%)
GASTROOESOPHAGEAL REFLUX DISEASE	0	0	0	1 (0.1%)	0	1 (0.0%)
ILEUS	0	0	0	1 (0.1%)	0	1 (0.0%)
OESOPHAGEAL PERFORATION	0	0	0	1 (0.1%)	0	1 (0.0%)
PANCREATITIS	0	0	0	0	1 (0.2%)	1 (0.0%)
PERITONITIS	0	0	0	0	1 (0.2%)	1 (0.0%)
PYLORIC STENOSIS	0	0	0	1 (0.1%)	0	1 (0.0%)
RECTAL BLEEDING	0	0	1 (0.1%)	0	0	1 (0.0%)
SMALL INTESTINAL OBSTRUCTION	0	0	0	1 (0.1%)	0	1 (0.0%)
VOMITING	1 (0.2%)	0	1 (0.1%)	0	0	1 (0.0%)
ABDOMINAL PAIN UPPER	1 (0.2%)	0	0	0	0	0

TOOTHACHE	0	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1 (0.1%)**	**0**	**8 (0.5%)**	**15 (1.0%)**	**1 (0.2%)**	**24 (0.6%)**
DISEASE PROGRESSION	0	0	4 (0.3%)	3 (0.2%)	0	7 (0.2%)
ASTHENIA	0	0	0	2 (0.1%)	0	2 (0.0%)
DEATH	0	0	0	2 (0.1%)	0	2 (0.0%)
IRRITABILITY	0	0	1 (0.1%)	1 (0.1%)	0	2 (0.0%)
OEDEMA PERIPHERAL	0	0	0	1 (0.1%)	1 (0.2%)	2 (0.0%)
SUDDEN DEATH	0	0	0	2 (0.1%)	0	2 (0.0%)
CHEST PAIN	1 (0.1%)	0	0	1 (0.1%)	0	1 (0.0%)
CYST	0	0	1 (0.1%)	0	0	1 (0.0%)
FATIGUE	0	0	1 (0.1%)	0	0	1 (0.0%)
GENERALISED OEDEMA	0	0	0	1 (0.1%)	0	1 (0.0%)
HYPOTHERMIA	0	0	0	1 (0.1%)	0	1 (0.0%)
INFLUENZA LIKE ILLNESS	0	0	0	1 (0.1%)	0	1 (0.0%)
OEDEMA	0	0	1 (0.1%)	0	0	1 (0.0%)
PYREXIA	0	0	0	1 (0.1%)	0	1 (0.0%)
HEPATOBILIARY DISORDERS	**2 (0.3%)**	**0**	**0**	**2 (0.1%)**	**0**	**2 (0.0%)**
CHOLECYSTITIS	2 (0.3%)	0	0	1 (0.1%)	0	1 (0.0%)
CHOLELITHIASIS	0	0	0	1 (0.1%)	0	1 (0.0%)
INFECTIONS AND INFESTATIONS	**0**	**1 (0.3%)**	**7 (0.5%)**	**11 (0.7%)**	**0**	**19 (0.5%)**
PNEUMONIA	0	0	2 (0.1%)	2 (0.1%)	0	4 (0.1%)
CELLULITIS	0	0	2 (0.1%)	1 (0.1%)	0	3 (0.1%)
URINARY TRACT INFECTION	0	0	1 (0.1%)	2 (0.1%)	0	3 (0.1%)
PYELONEPHRITIS	0	0	0	2 (0.1%)	0	2 (0.0%)
SEPSIS	0	0	0	2 (0.1%)	0	2 (0.0%)
ABSCESS	0	0	1 (0.1%)	0	0	1 (0.0%)
BRONCHITIS	0	0	1 (0.1%)	0	0	1 (0.0%)
DIARRHOEA INFECTIOUS	0	0	0	1 (0.1%)	0	1 (0.0%)
ERYSIPELAS	0	0	0	1 (0.1%)	0	1 (0.0%)
GASTROENTERITIS	0	0	1 (0.1%)	0	0	1 (0.0%)
HIV INFECTION	0	0	1 (0.1%)	0	0	1 (0.0%)
INFECTION	0	0	1 (0.1%)	0	0	1 (0.0%)
PERITONSILLAR ABSCESS	0	0	0	1 (0.1%)	0	1 (0.0%)
PROSTATIC ABSCESS	0	0	0	1 (0.1%)	0	1 (0.0%)
PULMONARY TUBERCULOSIS	0	0	1 (0.1%)	0	0	1 (0.0%)
UROSEPSIS	0	1 (0.1%)	0	0	0	1 (0.0%)
UPPER RESPIRATORY TRACT INFECTION	0	1 (0.1%)	0	0	0	1 (0.0%)
BRONCHITIS ACUTE	0	0	0	0	0	0
INFLUENZA	0	0	0	0	0	0

INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**2 (0.3%)**	**5 (1.4%)**	**13 (1.0%)**	**14 (0.9%)**	**2 (0.3%)**	**34 (0.8%)**
OVERDOSE	1 (0.1%)	0	5 (0.3%)	3 (0.2%)	0	8 (0.2%)
ANKLE FRACTURE	0	0	1 (0.1%)	3 (0.2%)	0	4 (0.1%)
INTENTIONAL OVERDOSE	1 (0.1%)	0	3 (0.2%)	0	1 (0.2%)	4 (0.1%)
UPPER LIMB FRACTURE	0	0	1 (0.1%)	1 (0.1%)	0	2 (0.0%)
FEMUR FRACTURE	0	1 (0.1%)	1 (0.1%)	0	0	2 (0.0%)
HIP FRACTURE	0	1 (0.1%)	1 (0.1%)	0	0	2 (0.0%)
ACCIDENT AT WORK	0	0	0	1 (0.1%)	0	1 (0.0%)
ACCIDENTAL OVERDOSE	0	0	1 (0.1%)	0	0	1 (0.0%)
ACCIDENTAL TRAUMA	0	0	1 (0.1%)	0	0	1 (0.0%)
ACCIDENT NOS	0	1 (0.1%)	0	0	0	1 (0.0%)
ALCOHOL POISONING	0	0	0	1 (0.1%)	0	1 (0.0%)
BURNS SECOND DEGREE	0	0	0	0	1 (0.2%)	1 (0.0%)
CONTUSION	0	0	0	1 (0.1%)	0	1 (0.0%)
FALL	0	1 (0.1%)	0	0	0	1 (0.0%)
FEMORAL NECK FRACTURE	0	0	0	1 (0.1%)	0	1 (0.0%)
FOOT FRACTURE	0	0	0	1 (0.1%)	0	1 (0.0%)
HAND FRACTURE	0	0	1 (0.1%)	0	0	1 (0.0%)
HUMERUS FRACTURE	0	0	1 (0.1%)	0	0	1 (0.0%)
FRACTURE PELVIS	0	1 (0.1%)	0	0	0	1 (0.0%)
POISONING DELIBERATE	0	0	0	1 (0.1%)	0	1 (0.0%)
SPINAL COMPRESSION FRACTURE	0	0	1 (0.1%)	0	0	1 (0.0%)
TIBIA FRACTURE	0	0	0	1 (0.1%)	0	1 (0.0%)
WOUND	0	0	0	1 (0.1%)	0	1 (0.0%)
HEAD INJURY	0	0	0	0	0	0
POISONING	0	0	0	0	0	0
INVESTIGATIONS	**0**	**0**	**2 (0.1%)**	**2 (0.1%)**	**0**	**4 (0.1%)**
BLOOD CREATINE PHOSPHOKINASE INCREASED	0	0	1 (0.1%)	0	0	1 (0.0%)
BLOOD PRESSURE INCREASED	0	0	0	1 (0.1%)	0	1 (0.0%)
HEPATIC ENZYME INCREASED	0	0	0	1 (0.1%)	0	1 (0.0%)
HIV TEST POSITIVE	0	0	1 (0.1%)	0	0	1 (0.0%)
METABOLISM AND NUTRITION DISORDERS	**1 (0.1%)**	**0**	**1 (0.1%)**	**5 (0.3%)**	**1 (0.2%)**	**7 (0.2%)**
DIABETES MELLITUS NON-INSULIN-DEPENDENT	0	0	0	2 (0.1%)	0	2 (0.1%)
ANOREXIA	0	0	0	1 (0.1%)	0	1 (0.0%)
DEHYDRATION	0	0	0	1 (0.1%)	0	1 (0.0%)
DIABETES MELLITUS	0	0	0	1 (0.1%)	0	1 (0.0%)
DIABETIC KETOACIDOSIS	0	0	0	1 (0.1%)	0	1 (0.0%)
HYPERGLYCAEMIA	0	0	0	0	1 (0.2%)	1 (0.0%)

HYPEROSMOLAR STATE	0	0	0	0	1 (0.2%)	1 (0.0%)
POLYDIPSIA	0	0	1 (0.1%)	0	0	1 (0.0%)
HYPONATRAEMIA	1 (0.1%)	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**0**	**0**	**0**	**3 (0.2%)**	**0**	**3 (0.1%)**
ARTHRALGIA	0	0	0	1 (0.1%)	0	1 (0.0%)
MUSCLE SPASMS	0	0	0	1 (0.1%)	0	1 (0.0%)
MUSCULOSKELETAL CHEST PAIN	0	0	0	1 (0.1%)	0	1 (0.0%)
BACK PAIN	0	0	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**0**	**0**	**1 (0.1%)**	**2 (0.1%)**	**1 (0.2%)**	**4 (0.1%)**
LUNG NEOPLASM MALIGNANT	0	0	0	0	1 (0.2%)	1 (0.0%)
RENAL CELL CARCINOMA STAGE UNSPECIFIED	0	0	0	1 (0.1%)	0	1 (0.0%)
RENAL NEOPLASM	0	0	1 (0.1%)	0	0	1 (0.0%)
UTERINE CANCER	0	0	0	1 (0.1%)	0	1 (0.0%)
NERVOUS SYSTEM DISORDERS	**3 (0.4%)**	**0**	**18 (1.2%)**	**20 (1.3%)**	**3 (0.5%)**	**41 (1.0%)**
CONVULSION	2 (0.3%)	0	3 (0.2%)	2 (0.1%)	0	5 (0.1%)
GRAND MAL CONVULSION	0	0	3 (0.2%)	1 (0.1%)	0	4 (0.1%)
SYNCOPE	1 (0.1%)	0	4 (0.3%)	0	1 (0.2%)	4 (0.1%)
AKATHISIA	0	0	2 (0.1%)	1 (0.1%)	0	3 (0.1%)
DYSTONIA	0	0	2 (0.1%)	1 (0.1%)	0	3 (0.1%)
PSYCHOMOTOR HYPERACTIVITY	0	0	0	2 (0.1%)	1 (0.2%)	3 (0.1%)
AUTISM	0	0	0	2 (0.1%)	0	2 (0.0%)
TREMOR	0	0	1 (0.1%)	1 (0.1%)	0	2 (0.0%)
BRAIN NEOPLASM	0	0	0	0	1 (0.2%)	1 (0.0%)
CEREBROVASCULAR STOKE	0	0	1 (0.1%)	0	0	1 (0.0%)
COMA	0	0	0	1 (0.1%)	0	1 (0.0%)
COORDINATION ABNORMAL	0	0	0	1 (0.1%)	0	1 (0.0%)
DEPRESSED LEVEL OF CONSCIOUSNESS	0	0	0	1 (0.1%)	0	1 (0.0%)
DISTURBANCE IN ATTENTION	0	0	1 (0.1%)	0	0	1 (0.0%)
DIZZINESS POSTURAL	0	0	0	1 (0.1%)	0	1 (0.0%)
DYSARTHRIA	0	0	0	1 (0.1%)	0	1 (0.0%)
EXTRAPYRAMIDAL DISORDER	0	0	0	1 (0.1%)	0	1 (0.0%)
HEADACHE	0	0	1 (0.1%)	0	0	1 (0.0%)
HEMIPARESIS	0	0	0	0	1 (0.2%)	1 (0.0%)
LOSS OF CONSCIOUSNESS	0	0	0	1 (0.1%)	0	1 (0.0%)
MOVEMENT DISORDER	0	0	0	1 (0.1%)	0	1 (0.0%)
MUSCLE RIGIDITY	0	0	0	1 (0.1%)	0	1 (0.0%)
OPTIC NEURITIS	0	0	0	1 (0.1%)	0	1 (0.0%)

RESTLESSNESS	0	0	0	1 (0.1%)	0	1 (0.0%)
TONIC CLONIC MOVEMENTS	0	0	0	1 (0.1%)	0	1 (0.0%)
BRADYKINESIA	0	0	0	0	0	0
COGWHEEL RIGIDITY	0	0	0	0	0	0
DROOLING	0	0	0	0	0	0
DYSKINESIA	0	0	0	0	0	0
GAIT DISTURBANCE	0	0	0	0	0	0
PARKINSONIAN GAIT	0	0	0	0	0	0
SOMNOLENCE	0	0	0	0	0	0
SPEECH DISORDER	0	0	0	0	0	0
TONGUE PARALYSIS	0	0	0	0	0	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	**0**	**0**	**1 (0.1%)**	**3 (0.2%)**	**0**	**4 (0.1%)**
ECTOPIC PREGNANCY	0	0	1 (0.1%)	1 (0.1%)	0	2 (0.1%)
PREGNANCY	0	0	0	2 (0.1%)	0	2 (0.1%)
PSYCHIATRIC DISORDERS	**41 (6.1%)**	**0**	**179 (12.0%)**	**303 (18.6%)**	**28 (4.5%)**	**510 (12.5%)**
SCHIZOPHRENIA	19 (3.2%)	0	60 (4.0%)	105 (6.4%)	11 (1.8%)	175 (4.3%)
PSYCHOTIC DISORDER	9 (1.5%)	0	51 (3.4%)	107 (6.6%)	12 (1.9%)	170 (4.2%)
SUICIDAL IDEATION	2 (0.3%)	0	11 (0.7%)	22 (1.4%)	2 (0.3%)	35 (0.9%)
ANXIETY	3 (0.5%)	0	12 (0.8%)	18 (1.1%)	0	30 (0.7%)
AGITATION	3 (0.5%)	0	11 (0.7%)	17 (1.0%)	1 (0.2%)	29 (0.7%)
DELUSION	0	0	8 (0.5%)	20 (1.2%)	0	28 (0.7%)
DEPRESSION	1 (0.2%)	0	7 (0.5%)	14 (0.9%)	2 (0.3%)	23 (0.6%)
SUICIDE ATTEMPT	0	0	8 (0.5%)	11 (0.7%)	1 (0.2%)	20 (0.5%)
HALLUCINATION	0	0	4 (0.3%)	9 (0.6%)	1 (0.2%)	14 (0.3%)
INSOMNIA	0	0	4 (0.3%)	10 (0.6%)	0	14 (0.3%)
ACUTE PSYCHOSIS	0	0	5 (0.3%)	6 (0.4%)	2 (0.3%)	13 (0.3%)
AGGRESSION	1 (0.2%)	0	4 (0.3%)	8 (0.5%)	0	12 (0.3%)
HALLUCINATION, AUDITORY	1 (0.2%)	0	6 (0.4%)	4 (0.2%)	0	10 (0.2%)
SCHIZOPHRENIA PARANOID TYPE	0	0	1 (0.1%)	7 (0.4%)	0	8 (0.2%)
CATATONIA	0	0	2 (0.1%)	5 (0.3%)	0	7 (0.2%)
HOSTILITY	0	0	1 (0.1%)	6 (0.4%)	0	7 (0.2%)
SCHIZOAFFECTIVE DISORDER	1 (0.2%)	0	2 (0.1%)	5 (0.3%)	0	7 (0.2%)
ABNORMAL BEHAVIOUR	0	0	2 (0.1%)	3 (0.2%)	0	5 (0.1%)
HOMICIDAL IDEATION	0	0	3 (0.2%)	2 (0.1%)	0	5 (0.1%)
RESTLESSNESS	0	0	0	4 (0.2%)	0	4 (0.1%)
SCHIZOPHRENIA, PARANOID TYPE	1 (0.2%)	0	2 (0.1%)	2 (0.1%)	0	4 (0.1%)
TENSION	0	0	1 (0.1%)	2 (0.1%)	1 (0.2%)	4 (0.1%)
COMPLETED SUICIDE	0	0	2 (0.1%)	1 (0.1%)	0	3 (0.1%)
DEPRESSED MOOD	1 (0.2%)	0	1 (0.1%)	2 (0.1%)	0	3 (0.1%)
EXCITABILITY	0	0	0	3 (0.2%)	0	3 (0.1%)

MANIA	0	0	0	2 (0.1%)	1 (0.2%)	3 (0.1%)
PARANOIA	1 (0.1%)	0	2 (0.2%)	0	1 (0.2%)	3 (0.1%)
SELF INJURIOUS BEHAVIOUR	0	0	1 (0.1%)	2 (0.1%)	0	3 (0.1%)
ADJUSTMENT DISORDER	0	0	0	2 (0.1%)	0	2 (0.0%)
HYPOMANIA	0	0	0	1 (0.1%)	1 (0.2%)	2 (0.0%)
ALCOHOL WITHDRAWAL SYNDROME	0	0	1 (0.1%)	0	0	1 (0.0%)
ALCOHOLISM	1 (0.2%)	0	1 (0.1%)	0	0	1 (0.0%)
CONFUSIONAL STATE	0	0	1 (0.1%)	0	0	1 (0.0%)
CRYING	0	0	0	1 (0.1%)	0	1 (0.0%)
DELIRIUM	0	0	1 (0.1%)	0	0	1 (0.0%)
EXHIBITIONISM	0	0	0	1 (0.1%)	0	1 (0.0%)
FACTITIOUS DISORDER	0	0	1 (0.1%)	0	0	1 (0.0%)
FEAR	0	0	0	1 (0.1%)	0	1 (0.0%)
GRANDIOSITY	0	0	0	1 (0.1%)	0	1 (0.0%)
HALLUCINATION, VISUAL	0	0	0	1 (0.1%)	0	1 (0.0%)
IDEAS OF REFERENCE	0	0	0	1 (0.1%)	0	1 (0.0%)
LIBIDO DECREASED	0	0	0	1 (0.1%)	0	1 (0.0%)
LOGORRHOEA	0	0	0	1 (0.1%)	0	1 (0.0%)
MAJOR DEPRESSION	0	0	0	0	1 (0.2%)	1 (0.0%)
MENTAL DISORDER	0	0	1 (0.1%)	0	0	1 (0.0%)
MOOD ALTERED	0	0	1 (0.1%)	0	0	1 (0.0%)
MOOD SWINGS	0	0	0	1 (0.1%)	0	1 (0.0%)
NEGATIVISM	0	0	0	1 (0.1%)	0	1 (0.0%)
OBSESSIVE-COMPULSIVE DISORDER	0	0	0	1 (0.1%)	0	1 (0.0%)
PANIC ATTACK	0	0	0	1 (0.1%)	0	1 (0.0%)
PERSECUTORY DELUSION	0	0	0	1 (0.1%)	0	1 (0.0%)
POST-TRAUMATIC STRESS DISORDER	0	0	1 (0.1%)	0	0	1 (0.0%)
PSYCHOMOTOR RETARDATION	0	0	0	1 (0.1%)	0	1 (0.0%)
SCREAMING	0	0	0	1 (0.1%)	0	1 (0.0%)
SEASONAL AFFECTIVE DISORDER	0	0	0	1 (0.1%)	0	1 (0.0%)
SOCIAL PHOBIA	0	0	0	1 (0.1%)	0	1 (0.0%)
STRESS	0	0	0	1 (0.1%)	0	1 (0.0%)
SUSPICIOUSNESS	0	0	1 (0.1%)	0	0	1 (0.0%)
THINKING ABNORMAL	0	0	0	1 (0.1%)	0	1 (0.0%)
ASSAULTIVE BEHAVIOR	1 (0.1%)	0	0	0	0	0
IMPULSE-CONTROL DISORDER	0	0	0	0	0	0
INTENTIONAL SELF-INJURY	0	0	0	0	0	0
SLEEP DISORDER	0	0	0	0	0	0
RENAL AND URINARY DISORDERS	**0**	**0**	**4 (0.3%)**	**0**	**0**	**4 (0.1%)**
RENAL FAILURE ACUTE	0	0	2 (0.1%)	0	0	2 (0.0%)
URINARY INCONTINENCE	0	0	1 (0.1%)	0	0	1 (0.0%)

URINARY RETENTION	0	0	1 (0.1%)	0	0	1 (0.0%)
DYSURIA	0	0	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**0**	**0**	**1 (0.1%)**	**4 (0.3%)**	**1 (0.2%)**	**6 (0.1%)**
POSTMENOPAUSAL HAEMORRHAGE	0	0	0	2 (0.1%)	0	2 (0.0%)
PRIAPISM	0	0	1 (0.1%)	1 (0.1%)	0	2 (0.0%)
GYNAECOMASTIA	0	0	0	0	1 (0.2%)	1 (0.0%)
MENORRHAGIA	0	0	0	1 (0.1%)	0	1 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**0**	**0**	**7 (0.5%)**	**4 (0.3%)**	**1 (0.2%)**	**12 (0.3%)**
ASTHMA	0	0	5 (0.3%)	1 (0.1%)	0	6 (0.1%)
DYSPNOEA	0	0	0	1 (0.1%)	1 (0.2%)	2 (0.0%)
PULMONARY EMBOLISM	0	0	2 (0.1%)	0	0	2 (0.0%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	0	0	1 (0.1%)	0	1 (0.0%)
HYPOXIA	0	0	0	1 (0.1%)	0	1 (0.0%)
PNEUMONIA ASPIRATION	0	0	0	1 (0.1%)	0	1 (0.0%)
RESPIRATORY FAILURE	0	0	0	1 (0.1%)	0	1 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**0**	**0**	**1 (0.1%)**	**2 (0.1%)**	**0**	**3 (0.1%)**
CONTUSION	0	0	0	1 (0.1%)	0	1 (0.0%)
DENGUE FEVER	0	0	0	1 (0.1%)	0	1 (0.0%)
ICHTHYOSIS	0	0	1 (0.1%)	0	0	1 (0.0%)
DRUG ERUPTION	0	0	0	0	0	0
ERYTHEMA MULTIFORME	0	0	0	0	0	0
SOCIAL CIRCUMSTANCES	**0**	**0**	**3 (0.2%)**	**3 (0.2%)**	**0**	**6 (0.1%)**
DRUG ABUSER	0	0	2 (0.1%)	1 (0.1%)	0	3 (0.1%)
POLYSUBSTANCE ABUSE	0	0	1 (0.1%)	1 (0.1%)	0	2 (0.1%)
VERBAL ABUSE	0	0	0	1 (0.1%)	0	1 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	**0**	**0**	**2 (0.1%)**	**1 (0.1%)**	**0**	**3 (0.1%)**
HIP ARTHROPLASTY	0	0	1 (0.1%)	0	0	1 (0.0%)
HOSPITALISATION	0	0	0	1 (0.1%)	0	1 (0.0%)
SHOULDER ARTHROPLASTY	0	0	1 (0.1%)	0	0	1 (0.0%)
SPINAL DECOMPRESSION	0	0	1 (0.1%)	0	0	1 (0.0%)
SURGERY	0	0	1 (0.1%)	0	0	1 (0.0%)
VASCULAR DISORDERS	**0**	**0**	**7 (0.5%)**	**4 (0.3%)**	**0**	**11 (0.3%)**
HYPOTENSION	0	0	3 (0.2%)	1 (0.1%)	0	4 (0.1%)
HYPERTENSION	0	0	2 (0.1%)	0	0	2 (0.0%)
HAEMATOMA	0	0	0	1 (0.1%)	0	1 (0.0%)

ORTHOSTATIC HYPOTENSION	0	0	1 (0.1%)	0	0	1 (0.0%)
PERIPHERAL VASCULAR DISORDER	0	0	0	1 (0.1%)	0	1 (0.0%)
THROMBOPHLEBITIS	0	0	0	1 (0.1%)	0	1 (0.0%)
VENOUS THROMBOSIS	0	0	1 (0.1%)	0	0	1 (0.0%)

Notes:
- Contains all patients / all exposures in the iloperidone development program. This is a merged table containing data from ISS Table 7.5.1 and ISS Appendix 5.
- Adverse events are coded using the MedDRA dictionary (Version 8.1).
- Patients experiencing the same Adverse Event multiple times will only be counted once for the corresponding Preferred Term based on the greatest extent of severity. Similarly, patients experiencing multiple adverse events within the same System Organ Class (SOC) will be counted only once for that same System Organ Class.
- Adverse Events are sorted alphabetically by SOC and within each SOC the Preferred Term is presented by decreasing order of total frequency in Combined Iloperidone Group.
- Percentages are based on the total number of patients within treatment/dose group.

APPENDIX 10.5.2: PERMANENT DISCONTINUATION OF TREATMENT DUE TO ADVERSE EVENTS IN THREE OR MORE ILOPERIDONE-TREATED PATIENTS, DOUBLE BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101

SOC [a] Preferred Term	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 5-20 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
N (%) of pts who dc'd due to TEAE	*32 (5.5%)*	*25 (5.3%)*	*24 (5.0%)*	*19 (4.9%)*	*68 (5.1%)*	*9 (7.6%)*	*19 (6.2%)*	*16 (10.7%)*
Gastrointestinal	**1 (0.2%)**	**1 (0.2%)**	**5 (1.0%)**	**2 (0.5%)**	**80.6%)**	**0**	**4 (1.3%)**	**1 (0.7%)**
Nausea	0	1 (0.2%)	2 (0.4%)	0	3 (0.2%)	0	1 (0.3%)	0
Nervous system	**6 (1.0%)**	**5 (1.1%)**	**6 (1.2%)**	**4(1.0%)**	**15 (1.1%)**	**3 (2.5%)**	**10 (3.3%)**	**6 (4.0%)**
Dizziness	2 (0.3%)	0	3 (0.6%)	1 (0.3%)	4 (0.3%)	0	3 (1.0%)	0
Syncope	0	1 (0.2%)	1 (0.2%)	1 (0.3%)	3 (0.2%)	0	1 (0.3%)	0
Psychiatric	**15 (2.6%)**	**11 (2.3%)**	**6 (1.2%)**	**3 (0.8%)**	**20 (1.5%)**	**4 (3.4%)**	**3 (1.0%)**	**7 (4.7%)**
Psychotic disorder	6 (1.0%)	3 (0.6%)	2 (0.4%)	1 (0.3%)	6 (0.4%)	2 (1.7%)	1 (0.3%)	3 (2.0%)
Schizophrenia	2 (0.3%)	1 (0.2%)	2 (0.4%)	0	3 (0.2%)	0	1 (0.3%)	0
Reproductive system & breast	**1 (0.2%)**	**1 (0.2%)**	**4 (0.8%)**	**3 (0.8%)**	**8 (0.6%)**	**0**	**3 (1.0%)**	**0**
Erectile dysfunction	0	1 (0.2%)	1 (0.2%)	1 (0.3%)	3 (0.2%)	0	1 (0.3%)	0
Respiratory, thoracic & mediastinal	**0**	**3 (0.6%)**	**1 (0.2%)**	**1 (0.3%)**	**5(0.4%)**	**0**	**0**	**1 (0.7%)**
Dyspnoea	0	1 (0.2%)	1 (0.2%)	1 (0.3%)	3 (0.2%)	0	0	0
Vascular disorders	**0**	**1 (0.2%)**	**4(0.8%)**	**2 (0.5%)**	**7 (0.5%)**	**0**	**0**	**0**
Orthostatic hypotension	0	1 (0.2%)	3 (0.6%)	1 (0.3%)	5 (0.4%)	0	0	0

Data Source: ISS Table 9.1.2
Table includes data from double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.
Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; TEAE=treatment-emergent adverse event; ZIP=ziprasidone.
Patients who experienced multiple AEs within the same SOC were counted only once for that same SOC.
Patients who experienced the same AE multiple times within the same SOC were counted only once for the corresponding Preferred Term based on the highest degree of relationship.
Adverse events sorted alphabetically by SOC; within each SOC, the preferred term is presented by decreasing order of frequency in the combined ILO group.
Percentages are based on the total number of patients within each treatment/dose group.
[a] Complete SOC names have been abbreviated because of space constraints.

APPENDIX 10.5.3: CRITERIA FOR DETERMINING POTENTIALLY CLINICALLY IMPORTANT LABORATORY TEST RESULTS

Analyte	Lower Limit	Upper Limit
BASOPHILS, (10E9/L)	0	0.2
BASOPHILS (PERCENT), (%)	0	2
EOSINOPHILS, (10E9/L)	0	0.45
EOSINOPHILS (PERCENT), (%)	0	7
GLYCOHEMOGLOBIN A1C, (% TL HB)	4.5	6.1
HEMATOCRIT, (l/L)	0.41 (Males) 0.35 (Females)	0.5 (Males) 0.46 (Females)
HEMOGLOBIN, (G/L)	138 (Males) 120 (Females)	172 (Males) 156 (Females)
LYMPHOCYTES, (10E9/L)	0.85	4.1
LYMPHOCYTES (PERCENT), (%)	16	46
MONOCYTES, (10E9/L)	0.2	1.1
MONOCYTES (PERCENT), (%)	0	12
NEUTROPHILS (BANDS), (10E9/L)	0	0.86
NEUTROPHILS (BANDS, PERCENT), (%)	0	8
NEUTROPHILS (SEGS), (10E9/L)	1.8	8
NEUTROPHILS (SEGS, PERCENT), (%)	40	75
NEUTROPHILS (TOTAL), (10E9/L)	1.5	8.8
NEUTROPHILS (TOTAL, PERCENT), (%)	48	73
PLATELET COUNT, (10E9/L)	130	400
RED BLOOD CELLS, (10E12/L)	4.4 (Males) 3.9 (Females)	5.8 (Males) 5.2 (Females)
WHITE BLOOD CELLS, (10E9/L)	3.8	10.8

ALBUMIN, (G/L)	32	50
ALKALINE PHOSPHATASE, (U/L)	20	125
BILIRUBIN (DIRECT), (µMOL/L)	0	6
BILIRUBIN (TOTAL), (µMOL/L)	0	22
CALCIUM, (MMOL/L)	2.12	2.56
CHLORIDE, (MMOL/L)	95	108
CHOLESTEROL (TOTAL), (MMOL/L)	0	5.15
CO2 (BICARBONATE), (MMOL/L)	20	32
CREATININE, (µMOL/L)	44	124
CREATININE PHOSPHOKINASE (CPK, CK), (U/L)	0 (Males) 0 (Females)	235 (Males) 190 (Females)
GLOBULIN, (G/L)	22	42
GLUCOSE, (MMOL/L)	3.3 (Fasting) 3.3 (Unknown)	6.1 (Fasting) 7.8 (Unknown)
HIGH DENSITY LIPOPROTEIN (MMOL/L)	0.9	N/A
INORGANIC PHOSPHORUS, (MMOL/L)	0.8	1.45
LDH, (U/L)	118 (Males) 122 (Females)	273 (Males) 220 (Females)
LOW DEN. LIPOPROT. (CALC), (MMOL/L)	0	3.35
MAGNESIUM, (MMOL/L)	0.65	1
POTASSIUM, (MMOL/L)	3.5	5.3
PROLACTIN, (µG/L)	2 (Males) 2 (Females)	18 (Males) 209 (Females)
SGOT (AST), (U/L)	0 (Males) 0 (Females)	38 (Males) 32 (Females)
SGPT (ALT), (U/L)	0 (Males) 0 (Females)	40 (Males) 31 (Females)
SODIUM, (MMOL/L)	135	146
THYROID STIMULATING HORMONE (TSH), (MU/L)	0.4	5.5
TOTAL PROTEIN, (G/L)	60	85
TRIGLYCERIDES, (MMOL/L)	0	2.24
UREA (BUN), (MMOL/L)	2.5	9
URIC ACID, (µMOL/L)	240 (Males) 150 (Females)	510 (Males) 450 (Females)

Analyte	Absolute Limit	Change from Baseline Limit
CALCIUM OXALATE CRYS	3+, 4+ (on Normal, 1+, 2+, 3+, 4+ scale)	>=2 grade increase
EPITHELIAL CELLS	3+, 4+ (on Normal, 1+, 2+, 3+, 4+ scale)	>=2 grade increase
SQUAMOUS EPI CELLS	5-10,10-15,15-25,25-50,50-100,>100	>=2 grade increase
URINE BACTERIA	3+, 4+ (on Normal, 1+, 2+, 3+, 4+ scale)	>=2 grade increase
URINE BILIRUBIN	3+, 4+ (on Normal, 1+, 2+, 3+, 4+ scale)	>=2 grade increase
URINE BLOOD	3+, 4+ (on Normal, 1+, 2+, 3+, 4+ scale)	>=2 grade increase
URINE GLUCOSE	3+, 4+ (on Normal, 1+, 2+, 3+, 4+ scale)	>=2 grade increase
URINE KETONES	3+, 4+ (on Normal, 1+, 2+, 3+, 4+ scale)	>=2 grade increase
URINE LEUKOCYTE ESTERASE	3+, 4+ (on Normal, 1+, 2+, 3+, 4+ scale)	>=2 grade increase
URINE NITRITE	Positive/Abnormal	Abnormal when normal at baseline
URINE PH	>=8	>=8 when 5-8 at baseline
URINE PROTEIN	3+, 4+ (on Normal, 1+, 2+, 3+, 4+ scale)	>=2 grade increase
URINE RED BLOOD CELLS	5-10,10-15,15-25,25-50,50-100,>100	>=2 grade increase
URINE SPECIFIC GRAVITY	1.03-<1.04,1.04-<1.05,>=1.05	>=1 grade increase
URINE UROBILINOGEN	Positive/Abnormal	Abnormal when normal at baseline
URINE WHITE BLOOD CELLS	5-10,10-15,15-25,25-50,50-100,>100	>=2 grade increase

APPENDIX 10.5.4: LABORATORY ANALYTES WITH VALUES OUTSIDE THE NORMAL RANGE, DOUBLE-BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101 (SAFETY POPULATION)

Laboratory Analyte	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Combined (N=1344)	HAL 5-20 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
Basophils (10e9/L)								
n [a]	532 (90.6%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	4 (0.8%)	2 (0.5%)	0	0	2 (0.2%)	0	1 (0.4%)	0
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Basophils (%)								
n [a]	534 (91.0%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	8 (1.5%)	4 (1.0%)	3 (0.7%)	4 (1.1%)	11 (0.9%)	1 (0.9%)	4 (1.4%)	0
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Eosinophils (10e9/L)								
n [a]	532 (90.6%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	15 (2.8%)	8 (2.0%)	6 (1.3%)	15 (4.0%)	29 (2.4%)	3 (2.7%)	3 (1.1%)	16 (11.3%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Eosinophils (%)								
n [a]	534 (91.0%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	16 (3.0%)	12 (3.0%)	9 (2.0%)	19 (5.1%)	40 (3.3%)	4 (3.6%)	3 (1.1%)	19 (13.4%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Hemoglobin (g/L)								
n [a]	533 (90.8%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	17 (3.2%)	2 (0.5%)	3 (0.7%)	5 (1.3%)	10 (0.8%)	0	1 (0.4%)	6 (4.2%)
Low [b]	45 (8.4%)	42 (10.4%)	47 (10.4%)	85 (22.8%)	174 (14.2%)	11 (9.8%)	17 (6.2%)	25 (17.6%)
High/Low [b]	0	0	0	0	0	0	0	0
Hematocrit (l/L)								
n [a]	529 (90.1%)	400 (85.1%)	451 (93.4%)	372 (95.1%)	1223 (91.0%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	25 (4.7%)	4 (1.0%)	1 (0.2%)	17 (4.6%)	22 (1.8%)	2 (1.8%)	1 (0.4%)	16 (11.3%)
Low [b]	30 (5.7%)	39 (9.8%)	57 (12.6%)	69 (18.5%)	165 (13.5%)	5 (4.5%)	17 (6.2%)	19 (13.4%)
High/Low [b]	0	0	0	0	0	0	0	0
Lymphocytes (10e9/L)								
n [a]	532 (90.6%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	21 (3.9%)	9 (2.2%)	9 (2.0%)	2 (0.5%)	20 (1.6%)	1 (0.9%)	5 (1.8%)	1 (0.7%)
Low [b]	10 (1.9%)	12 (3.0%)	19 (4.2%)	7 (1.9%)	38 (3.1%)	3 (2.7%)	2 (0.7%)	0
High/Low [b]	0	0	0	0	0	0	0	0

Lymphocytes (%)								
n [a]	534 (91.0%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	38 (7.1%)	25 (6.2%)	20 (4.4%)	20 (5.4%)	65 (5.3%)	5 (4.5%)	8 (2.9%)	11 (7.7%)
Low [b]	33 (6.2%)	21 (5.2%)	31 (6.8%)	28 (7.5%)	80 (6.5%)	11 (9.8%)	29 (10.5%)	8 (5.6%)
High/Low [b]	0	0	0	0	0	0	0	0
Monocytes (10e9/L)								
n [a]	532 (90.6%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	10 (1.9%)	13 (3.2%)	9 (2.0%)	4 (1.1%)	26 (2.1%)	6 (5.4%)	9 (3.3%)	0
Low [b]	25 (4.7%)	4 (1.0%)	6 (1.3%)	27 (7.3%)	37 (3.0%)	1 (0.9%)	1 (0.4%)	19 (13.4%)
High/Low [b]	0	0	0	0	0	0	0	0
Monocytes (%)								
n [a]	534 (91.0%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	14 (2.6%)	24 (6.0%)	16 (3.5%)	5 (1.3%)	45 (3.7%)	9 (8.0%)	9 (3.3%)	0
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Neutrophils, Total (10e9/L)								
n [a]	398 (67.8%)	401 (85.3%)	435 (90.1%)	114 (29.2%)	950 (70.7%)	112 (94.9%)	276 (90.2%)	0
High [b]	82 (20.6%)	46 (11.5%)	68 (15.6%)	24 (21.1%)	138 (14.5%)	21 (18.8%)	74 (26.8%)	0
Low [b]	20 (5.0%)	28 (7.0%)	25 (5.7%)	6 (5.3%)	59 (6.2%)	5 (4.5%)	5 (1.8%)	0
High/Low [b]	1 (0.3%)	0	0	0	0	1 (0.9%)	0	0
Neutrophils, Total (%)								
n [a]	398 (67.8%)	401 (85.3%)	435 (90.1%)	114 (29.2%)	950 (70.7%)	112 (94.9%)	276 (90.2%)	0
High [b]	51 (12.8%)	35 (8.7%)	60 (13.8%)	15 (13.2%)	110 (11.6%)	18 (16.1%)	50 (18.1%)	0
Low [b]	19 (4.8%)	20 (5.0%)	21 (4.8%)	2 (1.8%)	43 (4.5%)	5 (4.5%)	5 (1.8%)	0
High/Low [b]	0	0	0	0	0	0	0	0
Platelet Count, (10e9/L)								
n [a]	528 (89.9%)	398 (84.7%)	451 (93.4%)	372 (95.1%)	1221 (90.8%)	110 (93.2%)	272 (88.9%)	140 (93.3%)
High [b]	36 (6.8%)	15 (3.8%)	20 (4.4%)	22 (5.9%)	57 (4.7%)	4 (3.6%)	13 (4.8%)	7 (5.0%)
Low [b]	5 (0.9%)	5 (1.3%)	11 (2.4%)	5 (1.3%)	21 (1.7%)	2 (1.8%)	8 (2.9%)	2 (1.4%)
High/Low [b]	0	1 (0.3%)	0	0	1 (0.1%)	0	0	0
Red Blood Cells, (10e12/L)								
n [a]	533 (90.8%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	8 (1.5%)	2 (0.5%)	1 (0.2%)	8 (2.2%)	11 (0.9%)	2 (1.8%)	1 (0.4%)	3 (2.1%)
Low [b]	46 (8.6%)	76 (18.9%)	94 (20.7%)	63 (16.9%)	233 (19.0%)	18 (16.1%)	35 (12.7%)	10 (7.0%)
High/Low [b]	0	0	0	0	0	0	0	0
White Blood Cells, (10e9/L)								
n [a]	533 (90.8%)	402 (85.5%)	454 (94.0%)	372 (95.1%)	1228 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	89 (16.7%)	43 (10.7%)	54 (11.9%)	38 (10.2%)	135 (11.0%)	18 (16.1%)	63 (22.8%)	16 (11.3%)
Low [b]	23 (4.3%)	18 (4.5%)	20 (4.4%)	9 (2.4%)	47 (3.8%)	0	7 (2.5%)	4 (2.8%)
High/Low [b]	0	0	0	0	0	0	0	0
Glycohemoglobin A1C, (% IL HB)								
n [a]	128 (21.8%)	2 (0.4%)	19 (3.9%)	244 (62.4%)	265 (19.7%)	0	0	136 (90.7%)
High [b]	11 (8.6%)	0	1 (5.3%)	28 (11.5%)	29 (10.9%)	0	0	19 (14.0%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0

Data Source: ISS Table 24.1.2
Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.
HAL=haloperidol; ILO=iloperidone; n=number of patients with measurable value for each analyte; PBO=placebo; RIS=risperidone; ZIP=ziprasidone.
High and Low categories are based on worst value observed during the treatment period.
Categories High, Low, and High/Low are considered mutually exclusive.
[a] Percentages are based on the total number of patients within each treatment group.
[b] Percentages are based on the total number of observed patients within each treatment group.

Liver Function Analytes								
Albumin (g/L)								
n [a]	539 (91.8%)	407 (86.6%)	458 (94.8%)	375 (95.9%)	1240 (92.3%)	112 (94.9%)	277 (90.5%)	142 (94.7%)
High [b]	15 (2.8%)	2 (0.5%)	7 (1.5%)	9 (2.4%)	18 (1.5%)	1 (0.9%)	2 (0.7%)	7 (4.9%)
Low [b]	6 (1.1%)	14 (3.4%)	10 (2.2%)	2 (0.5%)	26 (2.1%)	2 (1.8%)	10 (3.6%)	1 (0.7%)
High/Low [b]	0	0	0	0	0	0	0	0
Alkaline Phosphatase (U/L)								
n [a]	539 (91.8%)	404 (86.0%)	457 94.6%)	376 (96.2%)	1237 (92.0%)	111 (94.1%)	277 (90.5%)	142 (94.7%)
High [b]	39 (7.2%)	32 (7.9%)	26 (5.7%)	11 (2.9%)	69 (5.6%)	17 (15.3%)	21 (7.6%)	13 (9.2%)
Low [b]	3 (0.6%)	2 (0.5%)	1 (0.2%)	0	3 (0.2%)	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Bilirubin (Total) (µmol/L)								
n [a]	509 (86.7%)	388 (82.6%)	419 (86.7%)	363 (92.8%)	1170 (87.1%)	112 (94.9%)	251 (82.0%)	142 (94.7%)
High [b]	16 (3.1%)	7 (1.8%)	11 (2.6%)	13 (3.6%)	31 (2.6%)	1 (0.9%)	4 (1.6%)	7 (4.9%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Bilirubin (Direct) (µmol/L)								
n [a]	138 (23.5%)	2 (0.4%)	19 (3.9%)	259 (66.2%)	280 (20.8%)	0	0	142 (94.7%)
High [b]	3 (2.2%)	0	0	2 (0.8%)	2 (0.7%)	0	0	0
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
SGOT (AST) (U/L)								
n [a]	539 (91.8%)	407 (86.6%)	458 (94.8%)	375 (95.9%)	1240 (92.3%)	112 (94.9%)	277 (90.5%)	141 (94.0%)
High [b]	73 (13.5%)	90 (22.1%)	86 (18.8%)	27 (7.2%)	203 (16.4%)	20 (17.9%)	45 (16.2%)	8 (5.7%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
SGPT (ALT) (U/L)								
n [a]	539 (91.8%)	407 (86.6%)	458 (94.8%)	375 (95.9%)	1240 (92.3%)	112 (94.9%)	277 (90.5%)	142 (94.7%)
High [b]	109 (20.2%)	121 (29.7%)	147 (32.1%)	86 (22.9%)	354 (28.5%)	29 (25.9%)	73 (26.4%)	22 (15.5%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Renal Function Analytes								
Urea (BUN), (mmol/L)								
n [a]	541 (92.2%)	407 (86.6%)	458 (94.8%)	376 (96.2%)	1241 (92.3%)	112 (94.9%)	278 (90.8%)	142 (94.7%)
High [b]	9 (1.7%)	5 (1.2%)	9 (2.0%)	3 (0.8%)	17 (1.4%)	5 (4.5%)	4 (1.4%)	2 (1.4%)
Low [b]	16 (3.0%)	4 (1.0%)	4 (0.9%)	25 (6.6%)	33 (2.7%)	1 (0.9%)	2 (0.7%)	14 (9.9%)
High/Low [b]	0	0	0	0	0	0	0	0
Creatinine, (µmol/L)								
n [a]	541 (92.2%)	407 (86.6%)	457 (94.6%)	376 (96.2%)	1240 (92.3%)	112 (94.9%)	278 (90.8%)	142 (94.7%)
High [b]	17 (3.1%)	6 (1.5%)	13 (2.8%)	6 (1.6%)	25 (2.0%)	6 (5.4%)	10 (3.6%)	6 (4.2%)
Low [b]	1 (0.2%)	1 (0.2%)	4 (0.9%)	0	5 (0.4%)	0	1 (0.4%)	0
High/Low [b]	0	0	0	0	0	0	0	0
Metabolic Function Analytes								
Cholesterol (Total) (mmol/L)								
n [a]	541 (92.2%)	407 (86.6%)	458 (94.8%)	376 (96.2%)	1241 (92.3%)	112 (94.9%)	278 (90.8%)	142 (94.7%)
High [b]	105 (19.4%)	42 (10.3%)	52 (11.4%)	140 (37.2%)	234 (18.9%)	16 (14.3%)	29 (10.4%)	60 (42.3%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Creatinine Phosphokinase (CPK, CK) (U/L)								
n [a]	539 (91.8%)	407 (86.6%)	457 (94.6%)	375 (95.9%)	1239 (92.2%)	112 (94.9%)	277 (90.5%)	142 (94.7%)
High [b]	194 (36.0%)	183 (45.0%)	184 (40.3%)	110 (29.3%)	477 (38.5%)	52 (46.4%)	95 (34.3%)	39 (27.5%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Globulin (g/L)								
n [a]	138 (23.5%)	2 (0.4%)	19 (3.9%)	259 (66.2%)	280 (20.8%)	0	0	142 (94.7%)
High [b]	0	0	0	0	0	0	0	2 (1.4%)
Low [b]	3 (2.2%)	0	0	8 (3.1%)	8 (2.9%)	0	0	2 (1.4%)
High/Low [b]	0	0	0	0	0	0	0	0
Glucose (mmol/L)								
n [a]	538 (91.7%)	404 (86.0%)	455 (94.2%)	373 (95.4%)	1232 (91.7%)	112 (94.9%)	273 (89.2%)	142 (94.7%)
High [b]	146 (27.1%)	165 (40.8%)	209 (45.9%)	105 (28.2%)	479 (38.9%)	45 (40.2%)	96 (35.2%)	31 (21.8%)
Low [b]	40 (7.4%)	18 (4.5%)	25 (5.5%)	18 (4.8%)	61 (5.0%)	12 (10.7%)	8 (2.9%)	8 (5.6%)
High/Low [b]	6 (1.1%)	8 (2.0%)	9 (2.0%)	6 (1.6%)	23 (1.9%)	4 (3.6%)	10 (3.7%)	0

High Density Lipoprotein (mmol/L)								
n [a]	138 (23.5%)	2 (0.4%)	19 (3.9%)	259 (66.2%)	280 (20.8%)	0	0	142 (94.7%)
High [b]	138 (100.0%)	2 (100.0%)	19 (100.0%)	259 (100.0%)	280 (100.0%)	0	0	142 (100.0%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
LDH (U/L)								
n [a]	538 (91.7%)	401 (85.3%)	453 (93.8%)	375 (95.9%)	1229 (91.4%)	111 (94.1%)	272 (88.9%)	141 (94.0%)
High [b]	29 (5.4%)	24 (6.0%)	31 (6.8%)	4 (1.1%)	59 (4.8%)	10 (9.0%)	18 (6.6%)	2 (1.4%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Low Density Lipoprotein (Calc) (mmol/L)								
n [a]	135 (23.0%)	2 (0.4%)	18 (3.7%)	248 (63.4%)	268 (19.9%)	0	0	135 (90.0%)
High [b]	45 (33.3%)	1 (50.0%)	5 (27.8%)	97 (39.1%)	103 (38.4%)	0	0	37 (27.4%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Prolactin (µg/L)								
n [a]	333 (56.7%)	289 (61.5%)	206 (42.7%)	247 (63.2%)	742 (55.2%)	93 (78.8%)	92 (30.1%)	137 (91.3%)
High [b]	39 (11.7%)	81 (28.0%)	76 (36.9%)	63 (25.5%)	220 (29.6%)	80 (86.0%)	86 (93.5%)	22 (16.1%)
Low [b]	1 (0.3%)	3 (1.0%)	0	0	3 (0.4%)	0	0	2 (1.5%)
High/Low [b]	0	0	0	0	0	0	0	0
Triglycerides (mmol/L)								
n [a]	541 (92.2%)	407 (86.6%)	457 (94.6%)	376 (96.2%)	1240 (92.3%)	112 (94.9%)	278 (90.8%)	142 (94.7%)
High [b]	131 (24.2%)	104 (25.6%)	128 (28.0%)	116 (30.9%)	348 (28.1%)	32 (28.6%)	70 (25.2%)	38 (26.8%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Thyroid Stimulating Hormone (TSH) (mU/L)								
n [a]	14 (2.4%)	16 (3.4%)	8 (1.7%)	19 (4.9%)	43 (3.2%)	2 (1.7%)	5 (1.6%)	10 (6.7%)
High [b]	0	1 (6.3%)	0	0	1 (2.3%)	0	0	0
Low [b]	0	1 (6.3%)	0	0	1 (2.3%)	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Uric Acid (µmol/L)								
n [a]	541 (92.2%)	407 (86.6%)	458 (94.8%)	376 (96.2%)	1241 (92.3%)	112 (94.9%)	278 (90.8%)	142 (94.7%)
High [b]	83 (15.3%)	97 (23.8%)	115 (25.1%)	25 (6.6%)	237 (19.1%)	24 (21.4%)	42 (15.1%)	2 (1.4%)
Low [b]	21 (3.9%)	6 (1.5%)	6 (1.3%)	17 (4.5%)	29 (2.3%)	2 (1.8%)	2 (0.7%)	10 (7.0%)
High/Low [b]	0	0	0	0	0	0	0	0
Electrolytes								
Calcium, (mmol/L)								
n [a]	541 (92.2%)	407 (86.6%)	457 (94.6%)	376 (96.2%)	1240 (92.3%)	112 (94.9%)	278 (90.8%)	141 (94.0%)
High [b]	36 (6.7%)	9 (2.2%)	20 (4.4%)	26 (6.9%)	55 (4.4%)	3 (2.7%)	14 (5.0%)	11 (7.8%)
Low [b]	7 (1.3%)	28 (6.9%)	13 (2.8%)	3 (0.8%)	44 (3.5%)	5 (4.5%)	9 (3.2%)	1 (0.7%)
High/Low [b]	0	0	0	0	0	0	0	0
Chloride, (mmol/L)								
n [a]	541 (92.2%)	407 (86.6%)	457 (94.6%)	376 (96.2%)	1240 (92.3%)	112 (94.9%)	278 (90.8%)	142 (94.7%)
High [b]	13 (2.4%)	2 (0.5%)	4 (0.9%)	30 (8.0%)	36 (2.9%)	0	3 (1.1%)	15 (10.6%)
Low [b]	6 (1.1%)	5 (1.2%)	5 (1.1%)	2 (0.5%)	12 (1.0%)	1 (0.9%)	4 (1.4%)	0
High/Low [b]	0	0	0	0	0	0	0	0
CO_2 (Bicarbonate), (mmol/L)								
n [a]	539 (91.8%)	407 (86.6%)	458 (94.8%)	375 (95.9%)	1240 (92.3%)	112 (94.9%)	277 (90.5%)	141 (94.0%)
High [b]	26 (4.8%)	32 (7.9%)	27 (5.9%)	2 (0.5%)	61 (4.9%)	12 (10.7%)	18 (6.5%)	0
Low [b]	14 (2.6%)	2 (0.5%)	4 (0.9%)	13 (3.5%)	19 (1.5%)	1 (0.9%)	3 (1.1%)	5 (3.5%)
High/Low [b]	0	0	0	0	0	0	0	0
Inorganic Phosphorus, (mmol/L)								
n [a]	538 (91.7%)	401 (85.3%)	454 (94.0%)	375 (95.9%)	1230 (91.5%)	111 (94.1%)	272 (88.9%)	142 (94.7%)
High [b]	35 (6.5%)	17 (4.2%)	14 (3.1%)	53 (14.1%)	84 (6.8%)	1 (0.9%)	11 (4.0%)	34 (23.9%)
Low [b]	5 (0.9%)	6 (1.5%)	8 (1.8%)	3 (0.8%)	17 (1.4%)	0	5 (1.8%)	2 (1.4%)
High/Low [b]	0	0	0	0	0	0	0	0
Magnesium, (mmol/L)								
n [a]	403 (68.7%)	405 (86.2%)	438 (90.7%)	117 (29.9%)	960 (71.4%)	112 (94.9%)	278 (90.8%)	0
High [b]	0	1 (0.2%)	1 (0.2%)	0	2 (0.2%)	0	0	0
Low [b]	0	1 (0.2%)	0	1 (0.9%)	2 (0.2%)	1 (0.9%)	0	0
High/Low [b]	0	0	0	0	0	0	0	0

Potassium, (mmol/L)								
n [a]	538 (91.7%)	401 (85.3%)	453 (93.8%)	374 (95.7%)	1228 (91.4%)	111 (94.1%)	272 (88.9%)	141 (94.0%)
High [b]	10 (1.9%)	2 (0.5%)	3 (0.7%)	3 (0.8%)	8 (0.7%)	3 (2.7%)	3 (1.1%)	6 (4.3%)
Low [b]	6 (1.1%)	3 (0.7%)	2 (0.4%)	1 (0.3%)	6 (0.5%)	1 (0.9%)	4 (1.5%)	1 (0.7%)
High/Low [b]	0	0	0	0	0	0	0	0
Sodium, (mmol/L)								
n [a]	541 (92.2%)	407 (86.6%)	457 (94.6%)	376 (96.2%)	1240 (92.3%)	112 (94.9%)	278 (90.8%)	142 (94.7%)
High [b]	7 (1.3%)	3 (0.7%)	9 (2.0%)	5 (1.3%)	17 (1.4%)	0	5 (1.8%)	2 (1.4%)
Low [b]	10 (1.8%)	5 (1.2%)	7 (1.5%)	12 (3.2%)	24 (1.9%)	1 (0.9%)	4 (1.4%)	2 (1.4%)
High/Low [b]	0	0	0	0	0	0	0	0

Data Source: ISS Table 25.1.2
Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.
HAL=haloperidol; ILO=iloperidone; n=number of patients with measurable value for each analyte; RIS=risperidone; ZIP=ziprasidone.
High and Low categories are based on worst value observed during the treatment period.
Values are presented as n (%). Percentages are calculated based on the number of patients with a normal baseline measurement and at least one postbaseline measurement. Only patients who had paired data are included.

Laboratory Analyte	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 5-20 mg/d (N=118)	RIS 4-8 mg/d (N =306)	ZIP 160 mg/d (N=150)
CALCIUM OXALATE CRYSTALS								
n	2	0	2	2	4	0	0	0
Post-Baseline								
3+, 4+	1 (50.0%)	0	0	0	0	0	0	0
Change from BL								
>=2 grade increase	0	0	0	0	0	0	0	0
EPITHELIAL CELLS								
n	0	0	0	0	0	0	0	0
Post-Baseline								
3+, 4+	0	0	0	0	0	0	0	0
Change from BL								
>=2 grade increase	0	0	0	0	0	0	0	0
SQUAMOUS EPI CELLS								
n	50	9	15	84	108	0	2	55
Post-Baseline								
5-10,10-15,15-25,25-50,50-100,>100	12 (24.0%)	6 (66.7%)	2 (13.3%)	12 (14.3%)	20 (18.5%)	0	1 (50.0%)	9 (16.4%)
Change from BL								
>=2 grade increase	8 (16.0%)	2 (22.2%)	1 (6.7%)	8 (9.5%)	11 (10.2%)	0	1 (50.0%)	7 (12.7%)
URINE BACTERIA								
n	9	1	0	12	13	0	0	7
Post-Baseline								
3+, 4+	4 (44.4%)	1 (100.0%)	0	7 (58.3%)	8 (61.5%)	0	0	4 (57.1%)
Change from BL								
>=2 grade increase	2 (22.2%)	0	0	4 (33.3%)	4 (30.8%)	0	0	1 (14.3%)
URINE BILIRUBIN								
n	392	397	434	116	947	112	272	0
Post-Baseline								
3+, 4+	0	0	0	0	0	0	0	0
Change from BL								
>=2 grade increase	0	0	0	0	0	0	0	0
URINE BLOOD								
n	529	399	453	374	1226	112	272	141
Post-Baseline								
3+, 4+	28 (5.3%)	23 (5.8%)	24 (5.3%)	8 (2.1%)	55 (4.5%)	11 (9.8%)	16 (5.9%)	4 (2.8%)
Change from BL								
>=2 grade increase	33 (6.2%)	21 (5.3%)	27 (6.0%)	9 (2.4%)	57 (4.6%)	10 (8.9%)	16 (5.9%)	6 (4.3%)

URINE GLUCOSE								
n	529	399	453	374	1226	112	272	141
Post-Baseline 3+, 4+	5 (0.9%)	13 (3.3%)	14 (3.1%)	6 (1.6%)	33 (2.7%)	1 (0.9%)	1 (0.4%)	0
Change from BL >=2 grade increase	4 (0.8%)	14 (3.5%)	8 (1.8%)	7 (1.9%)	29 (2.4%)	2 (1.8%)	2 (0.7%)	0
URINE KETONES								
n	529	399	453	374	1226	112	272	141
Post-Baseline 3+, 4+	4 (0.8%)	1 (0.3%)	1 (0.2%)	0	2 (0.2%)	0	0	0
Change from BL >=2 grade increase	7 (1.3%)	3 (0.8%)	3 (0.7%)	0	6 (0.5%)	1 (0.9%)	1 (0.4%)	0
URINE LEUKOCYTE ESTERASE								
n	0	0	0	0	0	0	0	0
Post-Baseline 3+, 4+	0	0	0	0	0	0	0	0
Change from BL >=2 grade increase	0	0	0	0	0	0	0	0
URINE NITRITE								
n	392	397	434	116	947	112	272	0
Post-Baseline Positive/Abnormal	27 (6.9%)	27 (6.8%)	23 (5.3%)	3 (2.6%)	53 (5.6%)	16 (14.3%)	13 (4.8%)	0
Change from BL Abnormal when normal at baseline	20 (5.1%)	25 (6.3%)	19 (4.4%)	2 (1.7%)	46 (4.9%)	14 (12.5%)	11 (4.0%)	0
URINE PH								
n	529	399	453	374	1226	112	272	141
Post-Baseline >=8	2 (0.4%)	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	0	1 (0.4%)	1 (0.7%)
Change from BL >=8 when 5-8 at baseline	2 (0.4%)	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	0	1 (0.4%)	1 (0.7%)
URINE PROTEIN								
n	529	399	453	374	1226	112	272	141
Post-Baseline 3+, 4+	1 (0.2%)	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	0	1 (0.4%)	0
Change from BL >=2 grade increase	3 (0.6%)	6 (1.5%)	5 (1.1%)	1 (0.3%)	12 (1.0%)	3 (2.7%)	5 (1.8%)	1 (0.7%)
URINE RED BLOOD CELLS								
n	184	23	76	283	382	12	31	141
Post-Baseline 5-10,10-15,15-25,25-50,50-100,>100	30 (16.3%)	10 (43.5%)	26 (34.2%)	17 (6.0%)	53 (13.9%)	8 (66.7%)	11 (35.5%)	7 (5.0%)
Change from BL >=2 grade increase	20 (10.9%)	5 (21.7%)	10 (13.2%)	8 (2.8%)	23 (6.0%)	5 (41.7%)	6 (19.4%)	6 (4.3%)
URINE SPECIFIC GRAVITY								
n	529	400	453	374	1227	112	272	141
Post-Baseline 1.03-<1.04,1.04-<1.05,>=1.05	69 (13.0%)	50 (12.5%)	50 11.0%)	14 (3.7%)	114 (9.3%)	13 (11.6%)	27 (9.9%)	7 (5.0%)
Change from BL >=1 grade increase	65 (12.3%)	42 (10.5%)	45 (9.9%)	14 (3.7%)	101 (8.2%)	10 (8.9%)	21 (7.7%)	5 (3.5%)
URINE UROBILINOGEN								
n	392	397	434	116	947	112	272	0
Post-Baseline Positive/Abnormal	3 (0.8%)	1 (0.3%)	3 (0.7%)	0	4 (0.4%)	1 (0.9%)	2 (0.7%)	0
Change from BL Abnormal when normal at baseline	3 (0.8%)	1 (0.3%)	3 (0.7%)	0	4 (0.4%)	0	2 (0.7%)	0
URINE WHITE BLOOD CELLS								
n	205	48	84	286	418	18	41	141
Post-Baseline 5-10,10-15,15-25,25-50,50-100,>100	59 (28.8%)	24 (50.0%)	41 (48.8%)	26 (9.1%)	91 (21.8%)	15 (83.3%)	20 (48.8%)	15 (10.6%)
Change from BL >=2 grade increase	29 (14.1%)	16 (33.3%)	18 (21.4%)	11 (3.8%)	45 (10.8%)	5 (27.8%)	8 (19.5%)	11 (7.8%)

Data Source: ISS Table 26.1.2
Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.
BL=baseline; HAL=haloperidol; ILO=iloperidone; n=number of patients with measurable value for each analyte; PBO=placebo; RIS=risperidone; ZIP=ziprasidone.
Percentages are based on the total number of observed patients within each treatment group.

APPENDIX 10.5.5: CRITERIA FOR DETERMINING POTENTIALLY CLINICALLY IMPORTANT VITAL SIGN RESULTS

Vital Sign	Lower Limit	Upper Limit
Pulse Rate (bpm)	≤50 bpm	≥120 bpm
	≥15 bpm decrease	≥15 bpm increase
	≤50 bpm and a decrease of ≥15 bpm	≥120 bpm and an increase of ≥15 bpm
Systolic Blood Pressure (mm Hg)	<=90 mm Hg	>=150 mm Hg
	>=10 mm Hg decrease	>=10 mm Hg increase
	<=90 mm Hg and a decrease of >=10 mm Hg	>=150 mm Hg and an increase of >=10 mm Hg
Diastolic Blood Pressure (mm Hg)	>=10 mm Hg decrease	>=10 mm Hg increase
	<=65 mm Hg	>=100 mm Hg
	<=65 mm Hg and a decrease of >=10 mm Hg	>=100 mm Hg and an increase of >=10 mm Hg
Temperature (°C)	<=33.1°C	>=38.3°C
		>=38.3°C and a change of >=1.1°C
Body weight change from baseline	Decrease of ≥7%	Increase of ≥7%

Fall in systolic blood pressure from supine position to 3 minute standing position > 20 mm Hg
Fall in diastolic blood pressure from supine position to 3 minute standing position > 15 mm Hg
Increase in heart rate from supine position to 3 minute standing position > 20 bpm

APPENDIX 10.5.6: NUMBER (%) OF PATIENTS WITH POTENTIALLY CLINICALLY IMPORTANT VITAL SIGN RESULTS IN THE DOUBLE-BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101

Pulse Rate Assessment	Placebo	ILO 4-8 mg/d	ILO 10-16 mg/d	ILO 20-24 mg/d	ILO Comb.	HAL 5-20 mg/d	RIS 4-8 mg/d	ZIP 160 mg/d
Number of patients [a]	581 (99.0%)	460 (97.9%)	480 (99.4%)	391 (100.0%)	1331 (99.0%)	118 (100.0%)	301 (98.4%)	149 (99.3%)
≥120 bpm	49 (8.4%)	156 (33.9%)	120 (25.0%)	142 (36.3%)	418 (31.4%)	23 (19.5%)	72 (23.9%)	17 (11.4%)
≥15 bpm increase	303 (52.2%)	344 (74.8%)	307 (64.0%)	277 (70.8%)	928 (69.7%)	75 (63.6%)	197 (65.4%)	90 (60.4%)
≤50 bpm	12 (2.1%)	5 (1.1%)	11 (2.3%)	4 (1.0%)	20 (1.5%)	0	8 (2.7%)	6 (4.0%)
≥15 bpm decrease	249 (42.9%)	181 (39.3%)	189 (39.4%)	133 (34.0%)	503 (37.8%)	60 (50.8%)	126 (41.9%)	64 (43.0%)
≥120 bpm and an increase of ≥15 bpm [b]	39 (6.7%)	146 (31.7%)	111 (23.1%)	132 (33.8%)	389 (29.2%)	21 (17.8%)	66 (21.9%)	15 (10.1%)
≤50 bpm and a decrease of ≥15 bpm [b]	5 (0.9%)	2 (0.4%)	8 (1.7%)	2 (0.5%)	12 (0.9%)	0	5 (1.7%)	3 (2.0%)

[a] Number of patients with at least one postbaseline vital signs assessment.
[b] Percentages are based on the total number of observed patients within each treatment group.

Patients With at Least 1 Post-Baseline Vital Signs Assessment [a]	581 (99.0%)	460 (97.9%)	480 (99.4%)	391 (100.0%)	1331 (99.0%)	118 (100.0%)	301 (98.4%)	149 (99.3%)
Systolic Blood Pressure (mm Hg) [b]								
>=150 mm Hg	127 (21.9%)	99 (21.5%)	110 (22.9%)	78 (19.9%)	287 (21.6%)	32 (27.1%)	76 (25.2%)	28 (18.8%)
>=10 mm Hg increase	422 (72.6%)	348 (75.7%)	328 (68.3%)	268 (68.5%)	944 (70.9%)	99 (83.9%)	232 (77.1%)	115 (77.2%)
<=90 mm Hg	58 (10.0%)	112 (24.3%)	95 (19.8%)	67 (17.1%)	274 (20.6%)	22 (18.6%)	36 (12.0%)	12 (8.1%)
>=10 mm Hg decrease	408 (70.2%)	370 (80.4%)	384 (80.0%)	295 (75.4%)	1049 (78.8%)	97 (82.2%)	226 (75.1%)	111 (74.5%)
≥150 mm Hg and an increase of ≥10 mm Hg	113 (19.4%)	88 (19.1%)	90 (18.8%)	69 (17.6%)	247 (18.6%)	27 (22.9%)	67 (22.3%)	28 (18.8%)
≤90 mm Hg and a decrease of ≥10 mm Hg	48 (8.3%)	105 (22.8%)	90 (18.8%)	61 (15.6%)	256 (19.2%)	20 (16.9%)	34 (11.3%)	12 (8.1%)
Diastolic Blood Pressure (mm Hg) [b]								
>=10 mm Hg increase	365 (62.8%)	294 (63.9%)	274 (57.1%)	215 (55.0%)	783 (58.8%)	91 (77.1%)	181 (60.1%)	96 (64.4%)
>=10 mm Hg decrease	388 (66.8%)	361 (78.5%)	365 (76.0%)	285 (72.9%)	1011 (76.0%)	84 (71.2%)	216 (71.8%)	83 (55.7%)
≥100 mm Hg	103 (17.7%)	81 (17.6%)	65 (13.5%)	24 (6.1%)	170 (12.8%)	30 (25.4%)	56 (18.6%)	21 (14.1%)
≤65 mm Hg	282 (48.5%)	320 (69.6%)	279 (58.1%)	228 (58.3%)	827 (62.1%)	73 (61.9%)	146 (48.5%)	61 (40.9%)
≥100 mm Hg and an increase of ≥10 mm Hg	83 (14.3%)	63 (13.7%)	50 (10.4%)	15 (3.8%)	128 (9.6%)	26 (22.0%)	46 (15.3%)	17 (11.4%)
≤65 mm Hg and a decrease of ≥10 mm Hg	219 (37.7%)	259 (56.3%)	236 (49.2%)	196 (50.1%)	691 (51.9%)	53 (44.9%)	121 (40.2%)	42 (28.2%)

Source: ISS Table 15.5.2, ISS Table 27.1.2
Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.
d = day; HAL = haloperidol; ILO = iloperidone; ILO Comb. = combined iloperidone; RIS = risperidone; ZIP = ziprasidone.
[a] Percentages are based on the total number of patients within each treatment group.
[b] Percentages are based on the total number of observed patients within each treatment group.

Temperature Assessment	Placebo	ILO 4-8 mg/d	ILO 10-16 mg/d	ILO 20-24 mg/d	ILO Comb.	HAL 5-20 mg/d	RIS 4-8 mg/d	ZIP 160 mg/d
Number of patients	579	460	480	391	1331	118	303	149
>=38.3°C	3 (0.5%)	4 (0.9%)	3 (0.6%)	1 (0.3%)	8 (0.6%)	2 (1.7%)	3 (1.0%)	1 (0.7%)
<=33.1°C	2 (0.3%)	1 (0.2%)	0	1 (0.3%)	2 (0.2%)	0	1 (0.3%)	0
>=38.3°C and a change of >=1.1°C	0	1 (0.2%)	1 (0.2%)	1 (0.3%)	3 (0.2%)	1 (0.8%)	1 (0.3%)	1 (0.7%)

Temperature as measured during any point during period of observation. C=Celsius; F=Fahrenheit.
Percentages are based on the total number of observed patients within each treatment group.
Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone.

Weight (kg)	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 5-20 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
Distribution of Percent Weight Change								
0-<7%	279 (48.4%)	277 (60.9%)	310 (64.4%)	252 (64.5%)	839 (63.2%)	63 (53.4%)	183 (60.6%)	100 (67.1%)
7-<10%	19 3.3%)	28 (6.2%)	29 (6.0%)	44 (11.3%)	101 (7.6%)	5 (4.2%)	22 (7.3%)	6 (4.0%)
10-<15%	6 (1.0%)	17 (3.7%)	23 (4.8%)	22 (5.6%)	62 (4.7%)	1 (0.8%)	12 (4.0%)	2 (1.3%)
15-<20%	0	3 (0.7%)	4 (0.8%)	3 (0.8%)	10 (0.8%)	0	2 (0.7%)	0
>=20%	0	1 (0.2%)	2 (0.4%)	3 (0.8%)	6 (0.5%)	0	0	0
>=7% increase	25 (4.3%)	49 (10.8%)	58 (12.1%)	72 (18.4%)	179 (13.5%)	6 (5.1%)	36 (11.9%)	8 (5.4%)
>=7% decrease	14 (2.4%)	10 (2.2%)	4 (0.8%)	1 (0.3%)	15 (1.1%)	3 (2.5%)	4 (1.3%)	2 (1.3%)
% Change at Endpoint (SD)	-0.0 (3.68)	1.8 (4.74)	2.5 (4.59)	3.3 (4.45)	2.5 (4.63)	0.2 (4.92)	1.8 (4.46)	1.4 (3.37)

Data Source: ISS Table 16.1.2, ISS Table 16.2.2, ISS Table 28.1.2
Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.
Percentages are based on the total number of observed patients within each treatment group.

Vital Signs	Placebo	ILO 4-8 mg/d	ILO 10-16 mg/d	ILO 20-24 mg/d	ILO Comb.	HAL 5-20 mg/d	RIS 4-8 mg/d	ZIP 160 mg/d
Study Group 2	(N=587)	(N=470)	(N=483)	(N=391)	(N=1344)	(N=118)	(N=306)	(N=150)
Patients with at Least 1 Postbaseline Assessment [a]	581 (99.0%)	460 (97.9%)	480 (99.4%)	391 (100.0%)	1331 (99.0%)	118 (100.0%)	301 (98.4%)	149 (99.3%)

Patients with Orthostatic Response [b]	334 (57.5%)	375 (81.5%)	343 (71.5%)	266 (68.0%)	984 (73.9%)	87 (73.7%)	194 (64.5%)	80 (53.7%)
Patients with Sustained Orthostasis [b]	107 (18.4%)	187 (40.7%)	167 (34.8%)	151 (38.6%)	505 (37.9%)	39 (33.1%)	81 (26.9%)	17 (11.4%)

Sustained orthostatic response is defined as: fulfilled criteria for orthostatic response based on either the original or updated definition, on three consecutive assessment visits during days 1 through 7, fulfilled criteria for orthostatic response on two consecutive assessment visits from day 7 or after, or discontinued due to ORTHOSTATIC HYPOTENSION and fulfilled criteria for orthostatic response at the last vital signs assessment.

Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone.

[a] Percentages are based on the total number of patients within each treatment group.

[b] Percentages are based on the total number of observed patients within each treatment group.

APPENDIX 10.5.7: CRITERIA FOR DETERMINING POTENTIALLY CLINICALLY IMPORTANT VALUES ECG RESULTS

QTcF interval ≥ 450 msec
QTcF interval ≥ 480 msec
QTcF interval ≥ 500 msec
Heart rate > 100 bpm
Heart rate < 50 bpm
PR interval > 200 msec
QRS interval >100 msec

APPENDIX 10.5.8: NUMBER (%) OF PATIENTS WITH POTENTIALLY CLINICALLY IMPORTANT ECG RESULTS IN THE DOUBLE-BLIND PHASE OF STUDIES 3000, 3004, 3005, AND 3101

QTcF Parameter	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 15 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
Fridericia's formula								
Mean (±SD) baseline value, msec	384.6 (22.12)	381.3 (21.92)	382.9 (23.71)	386.2 (21.37)	383.4 (22.5)	390.2 (20.24)	378.8 (22.75)	388 (18)
Mean (±SD) maximum value, msec	393.2 (22.22)	394.8 (21.54)	396.1 (22.89)	408.5 (22.76)	399.5 (23.2)	402.5 (19.92)	390.1 (21.59)	410.3 (21.85)
N (%) with QTc:								
≥450 msec, all patients	6 (1.1%)	18 (1.7%)	34 (2.3%)	17 (3.9%)	69 (2.3%)	6 (1.1%)	1 (0.4%)	8 (4.4%)
≥450 msec, females	5 (2.9%)	15 (3.8%)	18 (3.5%)	11 (11.2%)	44 (4.3%)	4 (2.1%)	1 (1.1%)	7 (15.2%)
≥450 msec, males	1 (0.3%)	3 (0.4%)	16 (1.7%)	6 (1.8%)	25 (1.3%)	2 (0.6%)	0	1 (0.7%)
≥480 msec, all patients	0	0	3 (0.7%)	0	3 (0.2%)	0	0	0
≥480 msec, females	0	0	1 (0.6%)	0	1 (0.3%)	0	0	0
≥480 msec, males	0	2 (0.3%)	12 (1.3%)	6 (1.8%)	20 (1.0%)	2 (0.6%)	0	2 (1.5%)
≥500 msec, all patients	0	0	0	0	0	0	0	0
≥500 msec, females	0	0	0	0	0	0	0	0
≥500 msec, males	0	0	4 (0.4%)	0	4 (0.2%)	0	0	0
N (%) with ≥15% increase from BL in QTc at any TP	17 (3.1%)	118 (10.9%)	217 (14.7%)	57 (13.1%)	392 (13.1%)	43 (8.1%)	16 (5.8%)	15 (8.2%)
N (%) with ≥30 msec change in QTc at any TP	107 (19.7%)	441 (40.6%)	757 (51.4%)	239 (55.1%)	1437 (48.0%)	198 (37.3%)	82 (29.7%)	91 (50.0%)
N (%) with ≥60 msec change in QTc at any TP	15 (2.8%)	96 (8.8%)	184 (12.5%)	53 (12.2%)	333 (11.1%)	38 (7.2%)	14 (5.1%)	14 (7.7%)

Data Source: ISS Table 17.6.2. Note that ISS Table 17.6.2 omits a parameter if there were no occurrences for that particular parameter in any treatment group.
Table includes data from all phases of Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101 and period 1 of Study 2328
BL=baseline; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; TP=time point; ZIP=ziprasidone

ECG Parameter	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 5-20 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
Heart Rate (bpm)								
Number of patients	548	407	447	376	1230	110	275	148
>100 beats per minute	69 (12.6%)	86 (21.1%)	78 (17.4%)	74 (19.7%)	238 (19.3%)	18 (16.4%)	59 (21.5%)	25 (16.9%)
>25% increase from baseline	105 (19.2%)	114 (28.0%)	101 (22.6%)	107 (28.5%)	322 (26.2%)	14 (12.7%)	79 (28.7%)	28 (18.9%)
>25% increase from baseline when heart rate >100 bpm	29 (5.3%)	43 (10.6%)	33 (7.4%)	36 (9.6%)	112 (9.1%)	5 (4.5%)	28 (10.2%)	9 (6.1%)
<50 beats per minute	9 (1.6%)	3 (0.7%)	5 (1.1%)	4 (1.1%)	12 (1.0%)	0	3 (1.1%)	0
>25% decrease from baseline	64 (11.7%)	31 (7.6%)	36 (8.1%)	23 (6.1%)	90 (7.3%)	8 (7.3%)	28 (10.2%)	12 (8.1%)
>25% decrease from baseline when a heart rate <50 bpm	2 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.3%)	3 (0.2%)	0	1 (0.4%)	0
PR Interval								
Number of patients	548	407	447	376	1230	110	273	148
>200 msec	24 (4.4%)	14 (3.4%)	19 (4.3%)	12 (3.2%)	45 (3.7%)	5 (4.5%)	8 (2.9%)	4 (2.7%)
>25% increase from baseline	11 (2.0%)	12 (2.9%)	12 (2.7%)	9 (2.4%)	33 (2.7%)	3 (2.7%)	7 (2.6%)	2 (1.4%)
>25% increase from baseline when PR >200 msec	4 (0.7%)	4 (1.0%)	4 (0.9%)	3 (0.8%)	11 (0.9%)	0	2 (0.7%)	0
QRS Interval								
Number of patients	547	407	447	376	1230	110	275	148
>100 msec	40 (7.3%)	31 (7.6%)	33 (7.4%)	32 (8.5%)	96 (7.8%)	15 (13.6%)	21 (7.6%)	7 (4.7%)
>25% increase from baseline	12 (2.2%)	4 (1.0%)	5 (1.1%)	6 (1.6%)	15 (1.2%)	1 (0.9%)	3 (1.1%)	1 (0.7%)
>25% increase from baseline when QRS >100 msec	3 (0.5%)	4 (1.0%)	3 (0.7%)	4 (1.1%)	11 (0.9%)	1 (0.9%)	2 (0.7%)	0

Data Source: ISS Table 30.1.2.
Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.
BL=baseline; Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; TP=time point; ZIP=ziprasidone.

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/s/

Michelle Chuen
6/13/2008 04:14:46 PM
MEDICAL OFFICER

Ni Aye Khin
6/25/2008 03:33:37 PM
MEDICAL OFFICER
See memo to file for additional comments and recommendations.

Review and Evaluation of Clinical Data
NDA #22-192

Sponsor:	Vanda Pharmaceuticals, Inc.
Drug:	Iloperidone Tablets
Indication:	Schizophrenia
Material Submitted:	Proposed Labeling
Correspondence Date:	April 18, 2008
Date Received:	April 18, 2008

I. Background

On 9/27/07, the sponsor submitted this NDA for the approval of iloperidone in the treatment of schizophrenia.

The undersigned reviewer completed a review recommending a Not Approvable action on 6/13/08. Since the Division will likely issue an Approvable letter, the undersigned reviewer was asked to review labeling for this NDA.

II. Clinical Data

The following comments are based on a review of the clinical sections of sponsor's proposed labeling as presented in their April 18, 2008 submission.

HIGHLIGHTS OF PRESCRIBING INFORMATION

The bullets should be modified to state

- "Risk of death in atypical antipsychotic-treated patients was 1.6 to 1.7 times that in placebo-treated patients. (5.1)
- Iloperidone is not approved for treatment of patients with Dementia-Related Psychoses. (5.1)"

HIGHLIGHTS OF PRESCRIBING INFORMATION/Indications and Usage
This section should be modified to state

b(4)

b(5)

Iloperidone is indicated for the treatment of schizophrenia. (1)"

20 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

X Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Michelle Chuen
7/1/2008 12:27:55 PM
MEDICAL OFFICER

Ni Aye Khin
7/8/2008 07:34:15 PM
MEDICAL OFFICER
I disagree with some of Dr. Chuen's labeling recommendations; see memo to file for additional comments.

Review and Evaluation of Clinical Data
NDA #22-192

Sponsor:	Vanda Pharmaceuticals
Drug:	Iloperidone Tablets
Indication:	Schizophrenia
Material Submitted:	120-Day Safety Update for Long-Term, Open-Label Phase of Study VP-VYV-683-3103
Correspondence Date:	January 23, 2008
Date Received:	January 28, 2008

I. Background

Iloperidone is a mixed 5-HT2A/D2 antagonist developed for the treatment of schizophrenia. Data from 9 controlled studies, including that for the 597 patients in the short-term, double-blind phase of Study VP-VYV-683-3101 (also known as Study 3101), were integrated to form the safety database for this NDA. This safety update focuses on data for the 173 patients who were treated with iloperidone in the long-term, open-label phase of Study 3101. Of note, the clinical safety cut-off date for the original NDA was December 4, 2006, while the clinical cut-off date for this safety update was May 4, 2007, after the database for Study 3101 had been locked (on March 21, 2007).

II. Data Source and Exposure

The short-term, double-blind phase of Study 3101 consisted of treatment with iloperidone 12 mg twice daily (24 mg/day), ziprasidone 80 mg twice daily (160 mg/day), or placebo for 28 days. All patients who completed the short-term, double-blind phase were eligible to enter the long-term, open-label phase, which consisted of a 7-day fixed titration period followed by a flexible maintenance dosing period—either 12 mg daily (12 mg/day) or 12 mg twice daily (24 mg/day)—for up to 24 weeks.

Of the 381 patients who completed the short-term, double-blind phase, 173 entered the long-term, open-label phase and 72 completed the study. The sponsor provided the following table, titled "Patient Disposition by Double-Blind Treatment Group—Study 3101 OLE (All Treated Patients)":

Number (%) of Patients Who:	Treatment Group			ILO Total
	ILO-ILO [a] n (%)	ZIP-ILO [a] n (%)	PBO-ILO [a] n (%)	n (%)
Completed short-term, double-blind phase	193	98	90	381
Entered long-term, open-label phase [b]	86 (44.6)	46 (46.9)	41 (45.6)	173 (45.4)
Completed the long-term, open-label phase [c]	33 (38.4)	17 (37.0)	22 (53.7)	72 (41.6)
Withdrew during the long-term, open-label phase [c]	53 (61.6)	29 (63.0)	19 (46.3)	101 (58.4)
Primary reason for withdrawal [d,e]				
Protocol deviation	1 (1.9)	1 (3.4)	0	2 (2.0)
Adverse event(s)	13 (24.5)	7 (24.1)	4 (21.1)	24 (23.8)
Lost to follow-up	11 (20.8)	6 (20.7)	1 (5.3)	18 (17.8)
Death	0	1 (3.4)	0	1 (1.0)
Patient withdrew consent	15 (28.3)	13 (44.8)	8 (42.1)	36 (35.6)
Unsatisfactory therapeutic effect	6 (11.3)	0	3 (15.8)	9 (8.9)
Other	7 (13.2)	1 (3.4)	3 (15.8)	11 (10.9)

Data Source: 3101 OLE CSR Post-text Table 7.1-1.

[a] Treatment groups (iloperidone, ziprasidone, and placebo) are those assigned in the short-term, double-blind phase. For example, ziprasidone/iloperidone represents a patient being assigned to ziprasidone during the short-term, double-blind phase and iloperidone during the long-term, open-label phase. In the long-term, open-label phase, all patients received iloperidone (12 mg/day or 24 mg/day).

[b] Percentages are based on the total number of patients who completed the short-term, double-blind phase in each treatment group.

[c] Percentages are based on the total number of patients who entered the long-term, open-label phase in each treatment group.

[d] The investigator determined the primary reason for withdrawal. Only one reason was recorded on the CRF.

[e] Percentages are based on the total number of patients who withdrew during long-term, open-label phase within each treatment group.

Of note, the mean modal dose of iloperidone during the long-term, open-label phase was 21.6 mg/day, and the mean duration of treatment was 103 days.

In this safety update, the exposure data from the long-term, open-label phase of Study 3101 was added to the integrated safety database from the NDA. Of the 173 patients who entered the long-term, open-label extension phase, 87 were newly exposed to iloperidone (i.e. they switched from double-blind placebo or ziprasidone). This increased the number of patients who received iloperidone in the integrated clinical studies from 3210 to 3297. The sponsor provided the following table, titled: "Duration of Treatment, Updated Safety Data—Study Group 1 (Safety Population).

Duration of Treatment Time period	Placebo (N = 587)	ILO 4-8 mg/d (N = 1227)	ILO 10-16 mg/d (N = 1562)	ILO 20-24 mg/d (N =508)	ILO Total (N = 3297)	HAL 5-20 mg/d (N = 546)	RIS 4-8 mg/d (N = 311)	ZIP 160 mg/d (N = 184)
Mean (±SD), days	26.0 (13.71)	209.5 (294.73)	293.4 (317.14)	80.6 (123.39)	229.4 (296.29)	175.0 (155.92)	66.1 (87.84)	20.0 (9.16)
Cumulative duration of treatment:								
>1 Week	507 (86.4%)	1006 (82.0%)	1521 (97.4%)	499 (98.2%)	3026 (91.8%)	499 (91.4%)	285 (91.6%)	168 (91.3%)
>2 Weeks	422 (71.9%)	902 (73.5%)	1436 (91.9%)	440 (86.6%)	2778(84.3%)	460 (84.2%)	251 (80.7%)	111 (60.3%)
>3 Weeks	364 (62.0%)	822 (67.0%)	1361 (87.1%)	339 (66.7%)	2522 (76.5%)	428 (78.4%)	234 (75.2%)	102 (55.4%)
>4 Weeks	225 (38.3%)	769 (62.7%)	1313 (84.1%)	214 (42.1%)	2296 (69.6%)	408 (74.7%)	224 (72.0%)	4 (2.2%)
>5 Weeks	193 (32.9%)	737 (60.1%)	1268 (81.2%)	199(39.25%)	2204 (66.8%)	394 (72.2%)	214 (68.8%)	0
>6 Weeks	35 (6.0%)	662 (54.0%)	1115 (71.4%)	179 (35.2%)	1956 (59.3%)	345 (63.2%)	96 (30.9%)	0
>3 Months	0	513 (41.8%)	893 (57.2%)	121 (23.8%)	1527 (46.3%)	284 (52.0%)	46 (14.8%)	0
>6 Months	0	404 (32.9%)	742 (47.5%)	64 (12.6%)	1210 (36.7%)	236 (43.2%)	36 (11.6%)	0
>12 Months	0	237 (19.3%)	441 (28.2%)	22 (4.3%)	700 (21.2%)	24 (4.4%)	6 (1.9%)	0

Data Source: ISS Table 31.1.1 and ISS Table 32.1.1.

Table includes data from all phases of Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101 and period 1 of Study 2328.

Duration of treatment was based on the patient's total exposure to any individual study drug. If a patient was exposed to multiple study drugs in a clinical study, then the patient has been represented in the safety analyses once for each drug. For example, if a patient was assigned initially to placebo in the short-term phase and reassigned to iloperidone in the long-term phase and/or the open-label extension, then this patient has been counted twice (once for each of the 2 study drugs) in the safety tabulations.

Of note, at the effective dose of 20-24 mg/day, only 64 patients were exposed for >6 months and only 22 patients were exposed for >12 months.

Also, with the addition of these 87 patients, exposure to the 20-24 mg/day dose increased from 452 to 508 patients, for an additional 39.55 patient years. The sponsor provided the following table, titled: "Cumulative Patient-Years of Exposure to Study Drug, Updated Safety Data—Study Group 1 (Safety Population).

Treatment Group	Number Treated	Cumulative Extent of Exposure (Patient-Years)
Placebo	587	41.71
Iloperidone [a]	3297	2070.31
4-8 mg/day	1227	703.66
10-16 mg/day	1562	1254.58
20-24 mg/day	508	112.07
Haloperidol	546	261.57
Risperidone	311	56.30
Ziprasidone	184	10.09

Data Source: ISS Table 33.1.1

Table includes data from all phases of Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101 and period 1 of 2328.

[a] The total dose a patient received was calculated as a function of the modal dose. The modal dose for the patient was based on the daily dose that the patient received most frequently during the phase of study. If there was no true modal dose (e.g., infrequent doses such as during titration), the highest dose received was conservatively chosen as the modal dose.

III. Adverse Events

Deaths

One death occurred during the long-term, open-label phase of Study 3101. Patient VP-VYV-683-112-0009, a 30-year-old man of Asian Indian decent, died suddenly on Study Day 65. He had received ziprasidone during the short-term, double-blind study phase and had been receiving open-label iloperidone for a total of 37 days when he died. Two days before his death, his dose of iloperidone was reduced from 24 mg/day to 12 mg/day due to mild restless and mild akathisia. The patient's family reported that on the day of his death, he went for a walk. About one-half hour after his return, he lost consciousness, and his breathing was labored. The family rushed the patient to a nearby hospital, where he was pronounced dead on arrival. The cause of death remains unclear—no autopsy was performed, and the patient was cremated. Of note, the patient was not a smoker and "did not have a history of anaphylaxis, allergy, asthma, physical disorder, or any drug abuse/dependence. There was no family history of sudden death or myocardial infarction." Therefore, this reviewer cannot rule out that this death was related to the study drug.

Of note, the sponsor did conduct a mortality analysis based on patient years of exposure for the integrated Phase 2/3 iloperidone clinical studies in the ISS database (not including the data from 120-Day Safety Update), including deaths during treatment or within 30 days of treatment discontinuation. Based on published results, the mortality per 100 patient years was lower in the combined iloperidone group compared with ziprasidone, quetiapine, and aripiprazole. In addition, the sponsor also conducted an analysis of the rate of sudden, unexpected deaths in the original iloperidone NDA safety database and

compared it to the sudden death rates for other antipsychotic drugs, as presented in the NDA clinical review for ziprasidone. In their analysis, iloperidone had a comparable rate of sudden, unexpected deaths to risperidone and a lower rate than that for sertindole, ziprasidone, olanzapine, and quetiapine.

Other Serious Adverse Events

Fourteen patients had a treatment-emergent serious adverse event. Most of these were related to exacerbation of underlying psychiatric disorders. The sponsor included the following table, titled: "Patient List of Nonfatal Serious Adverse Events—Study 3101 OLE."

Treatment at Onset	Patient Number	Age/Sex/ Race	Preferred Term	Start day/ End day	Drug Relation	Severity
Iloperidone/Iloperidone						
ILO 12 mg/day	005-0013	40/M/BL	Schizophrenia	119/127	Unrelated	Severe
	005-0027	41/M/BL	Major depression	107/118	Unrelated	Severe
ILO 24 mg/day	008-0002	49/F/WH	Schizophrenia	36/43	Unrelated	Severe
	008-0010	55/M/WH	Psychotic disorder	64/69	Unrelated	Severe
	019-0016	44/M/BL	Psychotic disorder	65/74	Unrelated	Severe
	019-0017	45/M/BL	Psychotic disorder	201/217	Unrelated	Severe
	019-0021	27/M/BL	Psychotic disorder	115/129	Unrelated	Severe
	019-0033	34/M/WH	Schizophrenia	82/90	Unrelated	Mild
	031-0005	38/M/BL	Schizophrenia	57/65	Unrelated	Moderate
Ziprasidone/Iloperidone						
Titration	012-0005	25/M/BL	Excoriation	34/ –	Unrelated	Moderate
			Periorbital hematoma	34/ –	Unrelated	Moderate
			Drug abuser	34/35	Unrelated	Moderate
ILO 24 mg/day	008-0007	48/M/BL	Psychotic disorder	97/104	Unrelated	Severe
	014-0029	28/M/WH	Suicidal ideation	76/84	Unrelated	Severe
Placebo/Iloperidone						
ILO 12 mg/day	005-0030	32/M/BL	Psychotic disorder	91/95	Unrelated	Moderate
ILO 24 mg/day	101-0001	21/M/AS	Dengue fever	103/122	Unrelated	Severe

Data Source: 3101 OLE CSR Post-text Filtered Listing 10.2.2-1.
All events are treatment emergent.
AM = American Indian or Alaska Native; AS = Asian; BL = Black American; F = female; ILO = iloperidone; M = male; NA = Native Hawaiian or other Pacific Island; OLE = open-label extension; OT = Other; WH = White

Of note, patient number 012-0005 received the excoriation and periorbital hematoma from a fall, but the reason for the fall is not given. The same day, he also used cocaine.

Adverse Events Leading to Permanent Discontinuation of Study Drug

Overall, adverse events led to permanent discontinuation of study drug in 12.1% of patients in the open-label treatment phase of Study 3101. The most frequent of such events were in the system-organ class of Psychiatric Disorders (11/173; 6.4%). The only events that led to treatment discontinuation in 1% or more of iloperidone-treated patients were drug abuse (2/173; 1.2%), headache (2/173, 1.2%), psychotic disorder (4/173, 2.3%), and schizophrenia (3/173, 1.7%). The sponsor included the following table, titled: "Adverse Events That Led to Withdrawal, by Double-Blind Treatment Group—Study 3101 OLE."

Body System/ Preferred Term [a]	ILO-ILO (N = 86) [b]	ZIP-ILO (N = 46) [b]	PBO-ILO (N = 41) [b]	ILO Total (N = 173)
N (%) withdrawn for AE	12 (14.0%)	8 (17.4%)	4 (9.8%)	24 (13.9%)
General disorders and administration site conditions	**0**	**1 (2.2%)**	**0**	**1 (0.6%)**
Sudden death	0	1 (2.2%)	0	1 (0.6%)
Injections and infestations	**0**	**0**	**1 (2.4%)**	**1 (0.6%)**
Dengue fever	0	0	1 (2.4%)	1 (0.6%)
Investigations	**1 (1.2%)**	**0**	**0**	**1 (0.6%)**
Glycosylated haemoglobin increased	1 (1.2%)	0	0	1 (0.6%)
Metabolism and nutrition disorders	**1 (1.2%)**	**0**	**0**	**1 (0.6%)**
Hyponatraemia	1 (1.2%)	0	0	1 (0.6%)
Musculoskeletal and connective tissue disorders	**1 (1.2%)**	**0**	**0**	**1 (0.6%)**
Muscle titghtness	1 (1.2%)	0	0	1 (0.6%)
Nervous system disorders	**1 (1.2%)**	**2 (4.3%)**	**1 (2.4%)**	**4 (2.3%)**
Headache	1 (1.2%)	1 (2.2%)	0	2 (1.2%)
Dizziness	0	1 (2.2%)	0	1 (0.6%)
Somnolence	0	0	1 (2.4%)	1 (0.6%)
Psychiatric disorders	**7 (8.1%)**	**3 (6.5%)**	**1 (2.4%)**	**11 (6.4%)**
Psychotic disorder	2 (2.3%)	1 (2.2%)	1 (2.4%)	4 (2.3%)
Schizophrenia	2 (2.3%)	1 (2.2%)	0	3 (1.7%)
Hallucination, auditory	1 (1.2%)	0	0	1 (0.6%)
Major depression	1 (1.2%)	0	0	1 (0.6%)
Schizophrenia, paranoid type	1 (1.2%)	0	0	1 (0.6%)
Suicidal ideation	0	1 (2.2%)	0	1 (0.6%)
Renal and urinary disorders	**1 (1.2%)**	**0**	**1 (2.4%)**	**2 (1.2%)**
Renal impairment	0	0	1 (2.4%)	1 (0.6%)
Urinary incontinence	1 (1.2%)	0	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	**0**	**1 (2.2%)**	**0**	**1 (0.6%)**
Throat tightness	0	1 (2.2%)	0	1 (0.6%)
Social circumstances	**1 (1.2%)**	**1 (2.2%)**	**0**	**2 (1.2%)**
Drug abuse	1 (1.2%)	1 (2.2%)	0	2 (1.2%)

Data Source: 3101 OLE CSR Post-text Table 10.1.4-1b

OLE = open-label extension; SOC = system-organ class

[a] SOCs are sorted alphabetically; within each SOC, the preferred term is presented by decreasing order of total frequency.

[b] Percentages are based on the total number of patients within the treatment group.

Patients experiencing the same AE multiple times are only counted once for the corresponding preferred term. Similarly, patients experiencing multiple AEs within the same SOC are counted only once for that SOC.

Treatment-emergent Adverse Events

As this study was an open-label extension, without a placebo control group, this reviewer went over the complete "Treatment Emergent Adverse Events" table to look for any clinically significant, unexpected (for this class of medications) findings. The only such finding was "hemoglobin decreased" in 16/173 (9.2% of the subjects). However, the sponsor did not provide, in any organized fashion, further information on who these subjects were and the degree of their decreased hemoglobin. Of note, this reviewer

informally discussed this finding with the primary reviewer. She is aware of this particular issue and plans to address it in her NDA review.

IV. Literature Search

As a sufficiently comprehensive literature search was lacking in the original NDA, the sponsor included one as part of the 120-Day Safety Update. This search was conducted on November 13, 2007 using the PubMed search engine to indentify any recent publications on iloperidone. The sponsor concludes that in this search, "no previously unreported adverse events were found. None of the publications in the literature search revealed any new safety concerns, or affected the known safety profile, of iloperidone." This reviewer briefly surveyed all the articles in the literature search (e.g. looking at abstracts and under adverse events, if present). Most of the articles involved the drug's pharmacology or pharmacokinetics. No new adverse events of any concern could be found in these articles.

V. Conclusions and Recommendations

Based on a review of the 120-Day Safety Update, there were no new safety findings that would preclude approval of this application. However, as the primary review team is aware, even with the additional 87 patients treated with iloperidone in the open-label extension of Study 3101, there is insufficient exposure at relevant doses (20-24 mg/day) in the safety database. Of note, during the open-label phase of Study 3101, an otherwise physically healthy 30-year-old man died suddenly for unclear reasons (no autopsy was performed). This reviewer cannot rule out that his death was related to study drug, such as from a drug-induced cardiac arrhythmia. Finally, under treatment-related adverse events, 9.2% of subjects had "hemoglobin decreased," but the sponsor does not provide any further analysis of these subjects. The primary reviewer, Dr. Michelle Chuen, is already aware of and plans to address this issue in her review.

Phillip D. Kronstein, M.D.
June 13, 2008

cc: HFD-130/ Kronstein
Khin
Laughren
Updegraff
Dubitsky

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/s/

Phillip D Kronstein
6/13/2008 01:19:16 PM
MEDICAL OFFICER

Ni Aye Khin
6/25/2008 03:36:59 PM
MEDICAL OFFICER
See memo to file for additional comments.

Interdisciplinary Review Team for QT Studies

Response to Request for Consultation: QT Study Review

IND or NDA	22-192
Generic Name	Iloperidone
Sponsor	Vanda Pharmaceuticals Inc.
Indication	Treatment of Schizophrenia
Dosage Form	Tablets
Drug Class	Psychotropic
Therapeutic Dose	Initial Treatment: 12 mg/day administered b.i.d. Maintenance Treatment: b(4)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not defined
Application Submission Date	27 November 2007
Review Classification	Standard NDA
Date Consult Received	29 November 2007
Clinical Division	DPP/HFD 130
PDUFA Date	27 July 2008

1 SUMMARY

1.1 Overall Summary of Findings

In this QT study the sponsor attempted to compare the effects of administering three doses (8 mg b.i.d., 12 mg b.i.d., and 24 mg QD) of iloperidone with ziprasidone (80 mg b.i.d.) and quetiapine (375 mg b.i.d.) on the QT interval. The effects of metabolic inhibition on iloperidone and the active comparators were also evaluated.

Iloperidone prolongs the QT interval. At all doses studied, the maximum mean increase in baseline-corrected QTcF was greater than 10 ms, the threshold for regulatory concern. In the presence of metabolic inhibition, there was further lengthening of the QTcF interval. However, the design of the study had significant limitations and as a result the QT-IRT finds that a ***precise estimate of the effect*** of administering iloperidone on the QT interval cannot be established.

The major limitations are as follows:

- This study was not a placebo-controlled study. There were two active controls, ziprasidone 80 mg b.i.d. and quetiapine 375 mg b.i.d., but the magnitude of their effects on the QT interval is not well characterized.
- All treatments were administered open-label. Thus, the study is subject to potential bias.

- Assay sensitivity could not be established. The study included two active comparators: quetiapine (375 mg b.i.d.) and ziprasidone (80 mg b.i.d.). Based on the FDA analysis of the exposure-response analysis for quetiapine in two other QT studies (Study A750-1001 in NDA 22,192 and Study R076477-SCH-1014 in NDA 21,999), it is expected that quetiapine will increase the QT interval in a concentration-dependent manner, with an approximate effect size of 7-10 ms for a mean C_{max} of 1,000 to 1,200 ng/ml quetiapine. In this study, quetiapine did not prolong the QT interval despite achieving mean steady-state peak concentration of 826 ng/ml. Therefore, our confidence in the estimated effect size of administering iloperidone on QTc is low.

  The QT-IRT does not have experience with ziprasidone and cannot establish assay sensitivity based on its effects on QTc.

- ECGs were not available for review.

1.2 QT Interdisciplinary Review Team's Comments

- While none of the safety events identified to be of particular importance per ICH E-14 guidelines occurred in this study, one patient on ILO 12 mg b.i.d. did experience pre-syncope and sinus bradycardia.
- ECG acquisition and interpretation in this study had several limitations.
  - ECGs were not recorded in triplicate
  - ECG waveforms were not sent to the ECG warehouse for review.
- We do not recommend using metabolic inhibition with ketoconazole or paroxetine to assess the effects of supratherapeutic iloperidone concentrations on the QT interval because 1) ketoconazole itself prolongs the QT interval; 2) the metabolic profile of iloperidone will change with CYP3A4 and CYP2D6 inhibition; and 3) iloperidone may change the metabolism of ketoconazole or paroxetine. Furthermore, since this study did not include a placebo control, the observed increases in ΔQTc in treatment periods 2 and 3 are confounded by the co-administration of paroxetine and ketoconazole.

2 PROPOSED LABEL

The sponsor proposed the following label:

5.0 WARNINGS AND PRECAUTIONS

5.2 QT Prolongation

b(4)

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

X Draft Labeling (b5)

_____ Deliberative Process (b5)

3 BACKGROUND

Iloperidone is a new chemical entity proposed for the treatment of schizophrenia. Iloperidone belongs to the chemical class of piperidinyl-benzisoxazole derivatives and has high (nM) affinity for $5HT_{2A}$/NEα1/NEα2c/D_2/D_3/$5HT_{1A}$ receptors in humans and acts as an antagonist at selected dopaminergic, serotoninergic, and adrenergic receptors. The sponsor believes that it has effective antipsychotic activity with reduced liability for extrapyramidal symptoms, akathisia, prolactin elevation, sedation and weight gain.

3.1 MARKET APPROVAL STATUS

Iloperidone is not approved for marketing in any country.

3.2 PRECLINICAL INFORMATION

Source: Non-clinical Summary

The in vitro effects of iloperidone and its metabolites P95 and P88 in comparison with risperidone and ziprasidone were examined on mammalian cells stably transfected with cloned cDNA of the cardiac ion channel hERG using whole cell patch-clamp recordings. Blockade of hERG currents in vitro is an indication of the potential for QTc prolongation clinically (Study 008167). All test articles produced rapid, reversible blockade of hERG currents. The block potency rank order was iloperidone > ziprasidone~ P88 > risperidone > P95. Assessment of the blockade at near-physiological temperature showed an increase of the IC50 value for the blockade for all test items except for risperidone. These data suggest that P95 is unlikely to contribute to the QT prolongation potential of iloperidone.

In dog Purkinje fibers paced at stimulation frequencies of 0.5 and 1 Hz, iloperidone and its metabolite P88 at a concentration of 0.1 µM and above prolonged action potential duration. At the highest concentration tested (10 µM), there appeared to be a depression of the plateau phase of the action potential. This may be attributed to a possible interaction with cardiac calcium channels at this concentration. There was also a reduction in maximum rate of depolarization at 3 Hz at this concentration, indicating a frequency-dependent interaction with cardiac sodium channels. When Purkinje fibers were exposed to P95 at concentration of 0.01, 0.1, 1 and 10 µM, prolongated action potential duration at 10 µM did not reach to the level of statistical significance; there was no prolongation seen at the concentration below or at 1 µM.

These data indicate that iloperidone and its metabolite P88 at free plasma concentrations of 0.1 µM and above are likely to have direct effects on the QRS complex, QT duration, and cardiac conduction. The metabolite P95 is less likely to have direct effects on the QRS complex or QT duration unless plasma concentrations in excess of 10 µM are reached.

Iloperidone was also found to have potential hypotensive and vasodilatory effects similar to those of clozapine in normotensive and hypertensive rats and in conscious and anesthetized dogs. These effects appear to be due at least in part to α1-adrenergic receptor blockade. Apart from a transient increase in heart rate observed in some studies, no other notable hemodynamic effects (eg, cardiac output changes or ECG findings) were noted in rats or dogs. Metabolites P88, P89, and P95 were also found to exert hemodynamic effects similar to iloperidone, including decreasing blood pressure.

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Integrated Summary of Clinical Safety

The safety profile of iloperidone is based primarily on the integrated safety data from 4439 adult patients with schizophrenia (3210 exposed to iloperidone) enrolled in the double-blind phase of four Phase 3, randomized, placebo-controlled studies. Integrated safety data from 1944 adult patients enrolled in 5 additional active-controlled studies or who participated in the open-label extension phase of the placebo-controlled studies have also been included.

Study Group 1 included all patients enrolled in any phase of all 9 controlled studies combined. Study Group 2 included patients enrolled only in the double-blind phase of one of the 4 placebo-controlled studies combined. Study Group 3 included patients enrolled in the double-blind phase of one of the 8 active- or placebo-controlled studies combined. Study Group 4 included patients who received iloperidone in the open-label extension phase of one of 7 of the double-blind, controlled studies.

In total, 23 patients (15 iloperidone, one placebo, 3 active-control [2 risperidone, 1 haloperidol] and 4 not randomized; including treatment-related and unrelated to treatment) died while participating in the Iloperidone Clinical Program. Most of the deaths (n=13) occurred during the long-term, double-blind, or open-label treatment phase (Table 59). Five deaths were suicides. An additional 3 patients treated with iloperidone died of a cardiac event (sudden Cardiac arrest, sudden death due to Cardio-respiratory failure or Cardiac failure). All 3 cardiac events leading to death were determined by the investigators to be unrelated to study drug. All other causes of deaths occurred in 1 patient each.

In Study Group 1, *cardiac adverse events* (composite term) occurred in 9.2% of patients in the combined iloperidone group, which was higher than in the comparator groups (range, 3.5% to 4.2%), but similar to that in the ziprasidone group (11.4%). Among the three iloperidone dose groups, cardiac adverse events were reported more frequently in patients receiving ILO 20-24 mg/day (19.2%) than either of the 2 lower doses (7.5% each). This pattern was observed in both Study Groups 2 and 3. In Study Group 4, patients who previously received risperidone had the highest incidence of cardiac adverse events (8.5%), and those who received placebo, the lowest (4.3%).

In Study Group 1, *orthostatic hypotension or hypotension* was reported as an adverse event in 3.0% and 1.7% of patients, respectively, in the combined iloperidone group.

In Study Group 1, *seizures* were uncommon. Thirteen patients (0.4%) in the combined iloperidone group had a seizure some time during treatment, similar to the comparator groups (0.2% to 0.3%), except for ziprasidone (ISS Table 21.1.1). No seizures were reported in that group. Seizure was considered by the investigator to be drug related in 8 iloperidone-treated patients.

Across the entire ISS database a subset analysis was performed on only those patients who had an increase from baseline in QTc interval (using Study Group 1). The results showed that the mean maximum QTc interval durations remained within normal limits and were comparable across treatment groups (ranging from 392.86 ms to 408.90 ms). Similarly, mean increases and mean percent changes from baseline to worst QTcF value were also comparable (ranging from approximately 18 ms to approximately 29 ms and 5.0% to 8.0% across treatment groups, respectively). Moreover, there was no clinically relevant dose-related increase in mean QTc duration or in mean percent change from baseline among the 3 iloperidone dose groups. This pattern was observed for both Study Groups 2 and Study Group 3. In Study Group 4, the mean QTc durations were similar across groups, irrespective of prior double-blind treatment and remained within normal limits (ranging from 398.73 ms to 405.46 ms). However, the mean change from baseline to worst QTcF value was highest for patients who previously received haloperidol (36.9 ms, 10.2%) and lowest for patients who previously received placebo (22.0 ms, 5.9%) during double-blind treatment. Although QTcF interval

prolongation did appear to be more likely to occur with longer exposure to active treatment, it also appeared that the maximum effect during open-label iloperidone treatment plateaued at ≤470 ms.

Across the entire ISS database, 2 patients each had 1 episode in which their QTcF interval exceeded 500 ms. Both patients were men receiving open-label ILO 10-16 mg/day. However, both episodes were associated with confounding factors. One patient had a QTcF interval of 507 ms after overdosing on iloperidone (438 mg over 4 days), with no cardiac sequelae. After being treated in the hospital for extrapyramidal symptoms, the patient was discharged and resumed iloperidone treatment for an additional 11 months. The second patient has a QTcF interval of 508 ms while being treated in the intensive care unit for septic shock.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of iloperidone's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted A TQT study report and associated electronic data sets. ECGs were not submitted to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Protocol Number and Title

Protocol ILO522 2328: A randomized, open-label, multicenter, 5-arm, safety evaluating the effect of oral iloperidone at doses of 8 mg b.i.d., 12 mg b.i.d., and 24 mg q.d. on QTc interval duration in the presence and absence of metabolic inhibition, relative to other antipsychotics (ziprasidone 80 mg b.i.d, and quetiapine 375 mg b.i.d., in the presence and absence of metabolic inhibition), in otherwise healthy patients diagnosed with schizophrenia or schizoaffective disorder.

4.2.2 Study Dates

November 27, 2001 to May 03, 2002

4.2.3 Objectives

The primary objective of the study is to characterize the effect of iloperidone at doses of 8 mg b.i.d. and 12 mg b.i.d. on the duration of the QTc interval in otherwise healthy patients diagnosed with schizophrenia or schizoaffective disorder.

The secondary objectives of this study were:

- to evaluate the effect of iloperidone on QTc interval duration when given as a 24 mg once-daily dose
- to evaluate the effect of iloperidone on QTc interval duration in the presence of inhibitors of iloperidone metabolism
- to evaluate the concentration-effect relationship of iloperidone and its primary metabolite (P88), on QTc interval duration

- to compare the effects of iloperidone on the QTc interval to the effects of the antipsychotics ziprasidone, quetiapine, and risperidone (following protocol Amendment 2, dated 09-Jan-2002, risperidone was removed from this comparison).

4.2.4 Study Description

4.2.4.1 Design

This was a multicenter, randomized, open-label, 5-arm study that included 5 periods: screening, taper, washout/baseline, treatment period 1 (dose escalation and steady state without metabolic inhibition), and treatment period 2 (addition of 1 metabolic inhibitor). Patients who received iloperidone underwent one additional period, treatment period 3, in which a second metabolic inhibitor was added.

Table 1. Study Design (Treatment phase)

Phase	Treatment phase		
Period	Treatment Period 1	Treatment Period 2	Treatment Period 3
Iloperidone 8 mg b.i.d.	Days 1-15	Days 16 – 23 (+paroxetine)	Days 24 – 28 (+paroxetine and ketoconazole)
Iloperidone 12 mg b.i.d.	Days 1-17	Days 18 –25 (+paroxetine)	Days 26 –30 (+paroxetine and ketoconazole)
Iloperidone 24 mg q.d.	Days 1-18	Days 19 –26 (+paroxetine)	Days 27 –31 (+paroxetine and ketoconazole)
Risperidone 4 mg b.i.d.	Days 1-13	Days 14 – 21 (+paroxetine)	-
Ziprasidone 80 mg b.i.d.	Days 1-10	Days 11 – 15 (+ketoconazole)	-
Quetiapine 375 mg b.i.d.	Days 1-12	Days 13 – 17 (+ketoconazole)	-

Note: following Amendment 2 (see Section 4.1), the risperidone treatment arm was removed from the trial.

(Source: Ilo522-2328-legacy report: Table 3-2, page 25)

4.2.4.2 Controls

The study did not include a placebo control. Antipsychotics ziprasidone and quetiapine were used as active controls. However, no formal hypotheses were specified with regard to the active controls.

4.2.4.3 Blinding

This study was an open-label study. However, a centralized blinded ECG reader was used in order to avoid any potential bias in interpretation of ECG results.

4.2.5 Treatment Regimen

4.2.5.1 Treatment Arms

The study included 5 treatment arms:

- Iloperidone Low (8 mg b.i.d.)

- Iloperidone High (12 mg b.i.d.)
- Iloperidone QD (24 mg q.d.)
- Quetiapine 375 mg b.i.d.
- Iloperidone 80 mg b.i.d.

Reviewer's Comment: Risperidone 4 mg b.i.d. was included originally, but removed under protocol amendment 2.

Dosing schedules for iloperidone and reference therapies are shown in Table 2 and Table 3.

Table 2: Dosing Schedule for Iloperidone

Day	Iloperidone LOW (8 mg b.i.d.)				Iloperidone HIGH (12 mg b.i.d.)				Iloperidone QD (24 mg q.d.)			
	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs
1	2	1	1		2	1	1		2	1	1	
2	2	1	1	1 ECG	2	1	1	1 ECG	2	1	1	1 ECG
3	4	2	2		4	2	2		4	2	2	
4	4	2	2		4	2	2		4	2	2	
5	8	4	4		8	4	4		8	4	4	
6	8	4	4		8	4	4		8	4	4	
7	12	6	6		12	6	6		12	6	6	
8	16 TD	8	8		16	8	8		12	12	-	
9	16	8	8		20	10	10		16	16	-	
10	16	8	8		24 TD	12	12		20	20	-	
11	16	8	8		24	12	12		24 TD	24	-	
12	16	8	8		24	12	12		24	24	-	
13	16	8	8	ECGs	24	12	12		24	24	-	
14	16	8	8	ECGs	24	12	12		24	24	-	
15	16	8	8	ECGs	24	12	12	ECGs	24	24	-	
16	16+P	8	8		24	12	12	ECGs	24	24	-	ECGs
17	16+P	8	8	1 ECG	24	12	12	ECGs	24	24	-	ECGs
18	16+P	8	8		24+P	12	12		24	24	-	ECGs
19	16+P	8	8		24+P	12	12	1 ECG	24+P	24	-	
20	16+P	8	8		24+P	12	12		24+P	24	-	1 ECG
21	16+P	8	8	ECGs	24+P	12	12		24+P	24	-	
22	16+P	8	8	ECGs	24+P	12	12		24+P	24	-	
23	16+P	8	8	ECGs	24+P	12	12	ECGs	24+P	24	-	
24	16+P +K	8	8		24+P	12	12	ECGs	24+P	24	-	ECGs
25	16+P +K	8	8	1 ECG	24+P	12	12	ECGs	24+P	24	-	ECGs
26	16+P +K	8	8	ECGs	24+P +K	12	12		24+P	24	-	ECGs
27	16+P +K	8	8	ECGs	24+P +K	12	12	1 ECG	24+P +K	24	-	
28	16+P +K	8	8	ECGs	24+P +K	12	12	ECGs	24+P +K	24	-	1 ECG
29	-	-	-		24+P +K	12	12	ECGs	24+P +K	24	-	ECGs
30	-	-	-		24+P +K	12	12	ECGs	24+P +K	24	-	ECGs
31	-	-	-						24+P +K	24	-	ECGs

TD = Target dose; P=paroxetine 20 mg q.d.; K=ketoconazole 200 mg b.i.d.
Note: Based on Amendment 2, the PM dose of ketoconazole was not given on the last day of study drug administration (see Section 4.1).
BOLD = Days of steady-state ECG evaluations

(Source: Ilo522-2328-legacy report: Table 3-2, page 25)

Table 3: Dosing Schedule for Reference Therapies

Day	Risperidone				Ziprasidone				Quetiapine			
	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs
1	2	1	1		40	20	20		50	25	25	
2	4	2	2	1 ECG	40	20	20	1 ECG	100	50	50	1 ECG
3	4	2	2		80	40	40		200	100	100	
4	6	3	3		80	40	40		300	150	150	
5	6	3	3		120	60	60		400	200	200	
6	8 TD	4	4		160 TD	80	80		500	250	250	
7	8	4	4		160	80	80		600	300	300	
8	8	4	4		160	80	80	ECGs	750 TD	375	375	
9	8	4	4		160	80	80	ECGs	750	375	375	
10	8	4	4		160	80	80	ECGs	750	375	375	ECGs
11	8	4	4	ECGs	160+ K	80	80		750	375	375	ECGs
12	8	4	4	ECGs	160+ K	80	80	1 ECG	750	375	375	ECGs
13	8	4	4	ECGs	160+ K	80	80	ECGs	750+ K	375	375	
14	8+P	4	4		160+ K	80	80	ECGs	750+ K	375	375	1 ECG
15	8+P	4	4	1 ECG	160+ K	80	80	ECGs	750+ K	375	375	ECGs
16	8+P	4	4		-	-	-		750+ K	375	375	ECGs
17	8+P	4	4		-	-	-		750+ K	375	375	ECGs
18	8+P	4	4		-	-	-		-	-	-	
19	8+P	4	4	ECGs	-	-	-		-	-	-	
20	8+P	4	4	ECGs	-	-	-		-	-	-	
21	8+P	4	4	ECGs	-	-	-		-	-	-	
22	-	-	-		-	-	-		-	-	-	
23	-	-	-		-	-	-		-	-	-	

TD = Target dose; P=paroxetine 20 mg q.d.; K=ketoconazole 200 mg b.i.d.
BOLD = Days of steady-state ECG evaluations

Note: Following Amendment 2, the risperidone treatment arm was removed, and the PM dose of ketoconazole was not given on the last day of study drug administration (see Section 4.1).

(Source: Ilo522-2328-legacy report: Table 3-6, page 35)

4.2.5.2 Sponsor's Justification for Doses

The current study, CILO522A2328, included doses of 8 mg b.i.d. and 12 mg b.i.d. in order to evaluate the effect of iloperidone on QTc at these higher doses. This study also evaluated the safety of 24 mg/d given q.d., as it was unknown whether higher peak concentrations and/or greater fluctuations in plasma concentrations would affect the QTc interval duration.

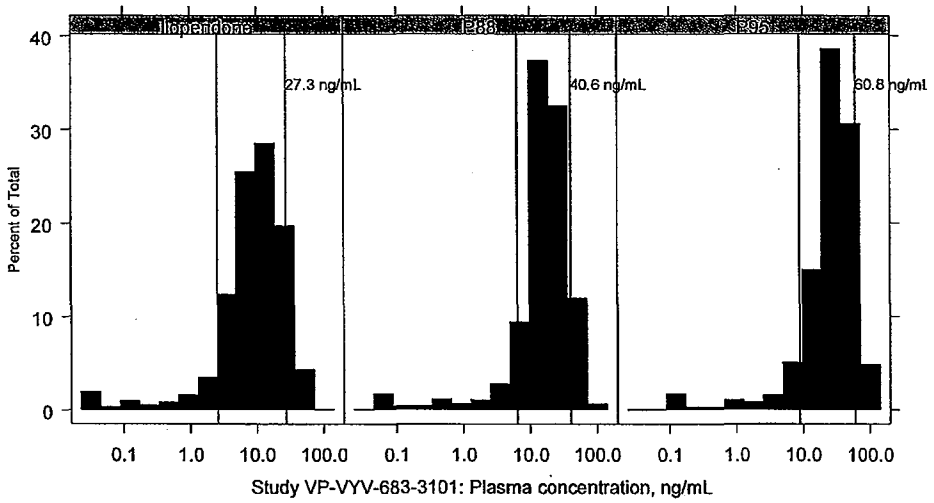
The inclusion of the three other antipsychotics served as reference points for the magnitude of observed QTc effects in this group of antipsychotic medications. Risperidone (8 mg daily) was initially included due to its reported limited effect on QTc (this treatment arm was removed by Amendment 2); quetiapine (750 mg daily) was included to represent the putative middle range of effect on QTc, and ziprasidone (160 mg daily) was included since it has the greatest reported effect on QTc among atypical antipsychotics. The doses of risperidone, quetiapine, and ziprasidone were based on recommendations from the manufacturers.

This study evaluated the effects of inhibition of both 3A4 and 2D6 in the iloperidone treatment arms by use of ketoconazole (200 mg b.i.d.) and paroxetine (20 mg q.d.), respectively. Ketoconazole was added as a metabolic inhibitor to the main P450 metabolic pathway of ziprasidone and quetiapine (CYP3A4).

Reviewer's Comments:

1. *The iloperidone doses are acceptable. The 8mg BID, 12mg BID and 24 mg QD doses would cover the expected clinical exposures. Figure 1 illustrates distribution of iloperidone, P88 and P95 concentration in VP-VYU-683-310, a randomized, double-blind, placebo- and ziprasidone-controlled, multi-center clinical trial to evaluate the efficacy, safety and tolerability of a 24 mg/day dose iloperidone given b.i.d. for 28 days to schizophrenic patients in acute exacerbation followed by a long-term treatment phase.*

Figure 1: Distribution of Iloperidone, P88 and P95 concentrations in VP-VYU-683-3101, a phase 3 clinical trial, after 12mg BID (24 mg/day) dosing. The vertical line represent 10th and 90th percentile. The number corresponds to the 90th percentile concentration.



2. *From a dose perspective, administration of ziprasidone 80 mg b.i.d. is acceptable as an active control. According to the label, the highest recommended dose to be used in patients with schizophrenia is [redacted] QTc prolongation is expected with this dose; however, the magnitude of QTc effect is not well characterized.* b(4)

3. *From a dose perspective, administration of quetiapine 375 mg b.i.d. is acceptable as an active control. According to the label, efficacy in schizophrenia was demonstrated in a dose range of [redacted] wever, QTc prolongation is not well characterized.*

4.2.5.3 Instructions with Regard to Meals

Patients took all antipsychotic study medication in the morning at approximately 8:00 a.m., and in the evening at approximately 6:30 p.m. (except for patients receiving ILO 24 mg q.d., who received the morning dose only). All study medications were taken with food, except on those days described below.

On the days of ECG assessments (Days -2, -1, and 0, and Steady-State Days [SSD] 1, 2, and 3 of each treatment period), patients did not eat within 3 hours prior to, or during, the T_{MAX} ECG assessments. Therefore, patients randomized to either iloperidone or risperidone did not eat breakfast (or ate breakfast only after morning ECGs were taken); those randomized to

ziprasidone did not eat lunch (or ate lunch only after afternoon ECGs were taken), in order to avoid the confounding effects of food on heart rate and QT duration around the T_{MAX} ECGs. Since blood concentrations of quetiapine are affected by food intake (maximum blood concentration achieved [Cmax] is increased with food intake) and ECGs recorded at T_{MAX} needed to be taken at 1, 1.5, and 2.5 hours after dosing, in order to maintain consistency of food restriction within 3 hours prior to the ECG recording, quetiapine was administered with a small, restricted, predefined liquid diet (e.g., Ensure®).

4.2.5.4 ECG and PK Assessments

Table 4: Assessment Schedule

Phase	Treatment phase												
Period	Treatment Period 1 [a]				Treatment Period 2 [b]				Treatment Period 3 [c] (iloperidone treated patients only)				
Evaluations / Day	D1 to DY[d]	SSD1	SSD2	SSD3	DX[e]-DY[d]	SSD1	SSD2	SSD3	DX[e]-DY[d]	SSD1	SSD2	SSD3	SC [f]
Meal Record		X	X	X		X	X	X		X	X	X	
Vital signs	Twice daily												X
Electrocardiogram	X[g]	XXX	XXX	XXXXXXXX X	X[g]	XXX	XXX	XXX	X[g]	XXX	XXX	XXX	X
Laboratory evaluation, Physical exam, CGI-S													X
IVRS call													X[h]
Pharmacokinetic (PK) sample		X[i]	X[i]			X[i]	X[i]			X[j]	X[j]		
Pregnancy test, urine drug screen													X
Concomitant medications	Daily	X	X	X	X	X	X	X	X	X	X	X	X
Drug administration record (DAR)	Daily	X	X	X	X	X	X	X	X	X	X	X	X[k]
Adverse events (AEs), serious AEs (SAEs)	Daily	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion (SC) form													X

[a] SSD1, 2, and 3 were the following study days for: ILO LOW=13,14,15; ILO HIGH=15, 16, 17; ILO QD=16, 17, 18; RIS=11, 12, 13; ZIP=8, 9, 10; QUET=10, 11, 12.

[b] Patients received one metabolic inhibitor in addition to the assigned treatment during this period: iloperidone- and (prior to Amendment 2; see Section 4.1) risperidone-treated patients received paroxetine 20 mg q.d., and ziprasidone- and quetiapine-treated patients received ketoconazole 200 mg b.i.d. Note: Based on Amendment 2 (see Section 4.1).), the PM dose of ketoconazole was not given on the last day of study drug administration. SSD1, 2, and 3 are the following study days for: ILO LOW=21, 22, 23; ILO HIGH=23, 24, 25; ILO QD=24, 25, 26; RIS=19, 20, 21; ZIP=13, 14, 15; QUET=15, 16, 17.

[c] In addition to paroxetine, patients randomized to iloperidone received ketoconazole 200 mg b.i.d. during this period. Patients randomized to any other treatment did NOT enter this period. During this period, SSD1, 2, and 3 were the following study days for: ILO LOW=26, 27, 28; ILO HIGH=28, 29, 30; ILO QD = 29, 30, 31.

[d] Day Y (DY) is the day immediately prior to SSD1 of this period. The corresponding study day is dependent on treatment assignment (see Tables 3-3 and 3-4).

[e] Day X (DX) is the day immediately following SSD3 of the prior period. The corresponding study day is dependent on treatment assignment (see Tables 3-3 and 3-4).

[f] SC=study completion evaluation conducted the morning following SSD3 of Period 2 or 3, depending on treatment assignment, or at premature discontinuation. Quetiapine, ziprasidone, and risperidone-treated patients had study completion evaluations performed the morning following SSD3 of Period 2. Iloperidone-treated patients had study completion performed the morning following SSD3 of period 3.

[g] One ECG was performed on the second day of each period (ILO HIGH=Days 2, 19, and 27; ILO LOW=Days 2, 17, 25; ILO QD=Days 2, 20, 28; and RIS=Days 2, 15; ZIP=Days 2, 12; QUET=Days 2, 14)

[h] The IVRS was called to report patient completion or discontinuation.

[i] 3 blood samples drawn from patients in the ILO group, 2 from patients in the ZIP, QUET, and (prior to Amendment 2; see Section 4.1) RIS groups.

[j] Three blood samples for pharmacokinetic analysis were drawn from patients in the iloperidone group.

[k] Performed only at premature discontinuation.

(Source: Ilo522-2328-legacy report: Table 3-8, page 40)

4.2.5.5 Baseline

The baseline QTc value was obtained by averaging all QTc values corresponding to the T_{max} of the compound on Days -2, -1, and 0.

4.2.6 ECG Collection

Multiple ECG measurements were taken at baseline and during 3 consecutive days at the steady state of all drugs administered, and during steady state after adding metabolic inhibitor(s). Baseline and post-baseline ECG measurements were taken at the same time of the day. On the 3 consecutive days of Periods 1, 9 ECGs were collected to allow for evaluation of circadian variations. A central reader who was blind to patient randomization evaluated all ECGs using a manual high-resolution analysis of the ECG interval measurements.

The primary analysis compared 3 ECGs per day taken on each of 3 consecutive days at the T_{max} of the given compound to 3 ECGs per day taken on each of 3 consecutive days at baseline. A separate analysis was conducted to compare 3 ECGs per day taken on each of 3 consecutive days around the T_{MAX} after adding the selected metabolic inhibitor(s) of the given compound to 3 ECGs per day taken on each of 3 consecutive days at baseline. Additional ECG measurements were taken on Day 0 and Steady-State Day 3 of Period 1 in order to compare the change from baseline to endpoint of the specified antipsychotic medication on QTc throughout the day, without regard to the C_{max} of the compounds. In addition, ECGs were taken during medication titration for safety purposes, but were not used for purposes of analysis.

Reviewer's Comment: ECG readers were only blinded to randomization. No triplicate ECGs were taken. ECGs were not sent to the ECG warehouse for review.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

The patient population for this study included patients who were diagnosed with schizophrenia or schizoaffective disorder but were not suffering from acute exacerbation of the disease. They were 18-65 years of age, 71-72% males in each group, with a normal baseline ECG.

Of the 188 randomized patients, eight withdrew before receiving study medication, and 180 patients received at least 1 dose of study medication. Of the 188 patients that were randomized, *149* completed the study (79%). Five patients were randomized to risperidone - this arm was removed following Amendment 2 of the protocol. The reasons for discontinuation in any group were treatment emergent AE's, treatment unsatisfactory, withdrawal of consent and protocol violation. Overall, 2 patients who received study medication were discontinued as a result of protocol violations; one patient was randomized to quetiapine 375 mg b.i.d. and one patient was randomized to risperidone 4 mg b.i.d. Additionally, 2 patients were discontinued for protocol violations before receiving study medication (both were randomized to iloperidone 8 mg b.i.d). Nine patients experienced AEs that lead to premature discontinuation. Of the 22 patients who withdrew consent, 19 belonged to the various iloperidone treatment groups.

Reviewer's Comment: There were more discontinuations due to withdrawal of consent after receiving study treatment in the iloperidone groups.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The sponsor's primary analysis compared 3 ECGs per day taken on each of 3 consecutive days at the T_{max} of the given compounds to 3 ECGs per day taken on each of 3 consecutive days at baseline. The primary variable of interest was the QTc change at T_{max} from baseline to steady state of treatment period 1. The baseline QTc value was obtained by averaging all QTc values corresponding to the T_{max} of the compound on Days –2, –1, and 0. The QTc value for the steady state was also averaged over all QTc values around T_{max} on Steady-State Day (SSD1), Steady-State Day 2 (SSD2), and Steady-State Day 3 (SSD3) of treatment period 1. The primary analysis used the Fridericia's method to correct the QT duration for heart rate.

The primary variable was analyzed by an ANCOVA model with adjusted baseline QTC value as a covariate and treatment and gender as class variables. The adjusted baseline QTc value for

each patient was obtained by subtracting the mean of all original baseline values around T_{max} for all patients from that patient's baseline QTc value.

The primary QTc population for the QTc analysis were all patients who had at least 50% ($\geq$ 5) of the QTc evaluations on days SSD1, SSD2, and SSD3 at T_{max} during treatment period 1 and at least half ($\geq$ 5) of the QTc evaluations around times that corresponded to the T_{max} for each compound at baseline (Days –2, –1, and 0).

The sponsor's primary analysis is presented in Table 5. The table reported the raw means (unadjusted for covariates) as well as the least square means. The least square means are based on the ANCOVA model with adjusted baseline QTc as a covariate, gender and treatment as factors. The least square means did not differ substantially from the raw means.

Table 5. Summary statistics of QTcF (Fridericia correction) change (95% CI) from baseline to steady state at T_{max} during Treatment Period 1 (Primary QTc population)

	Ilo 8 mg	Ilo 12 mg	Ilo 24 mg	Zip	Quet
Sample size	28	34	31	32	33
Baseline					
Raw mean ± SD	385.9 ± 16.4	386.5 ± 17.1	379.0 ± 14.7	383.4 ± 13.5	383.2 ± 18.9
Change in QTcF					
Raw mean ± SD	8.5 ± 10.5	9.0 ± 12.5	15.4 ± 11.7	9.6 ± 11.0	1.3 ± 11.1
LS mean*	9.1	9.7	14.6	9.7	1.3
(95% CI for LS mean)	(4.9, 13.3)	(5.8, 13.6)	(10.6, 18.9)	(5.7, 13.7)	(-2.5, 5.2)

* The least square means and confidence intervals are provided by the reviewer. The model included risperidone group that was dropped according to Protocol Amendment 2. These results are slightly different than the results reported on Table 9.2.1-2, page 308 as the sponsor's results included two additional patients from the secondary QTc population)\

(Source: Ilo522-2328-legacy report: Table 9-1, page 57)

4.2.7.2.2 Categorical Analysis

No patient experienced a QTc of $\geq$ 500 ms during the study. Number of patients with QTc increase from baseline to steady state at T_{max} of $\geq$ 30 and 60 ms during treatment periods 1, 2, and 3 are presented in Table 6

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Table 6. Number (%) of Patients with QTc Increase from baseline to Steady-State at T_{max} of ≥ 30 and 60 ms during Treatment Periods 1, 2, and 3

	ILO 8 mg b.i.d.		ILO 12 mg b.i.d.		ILO 24 mg q.d.		ZIP 80 mg b.i.d.		QUET 375 mg b.i.d.	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Treatment Period 1										
Increase ≥ 30 msec										
Fridericia	29	9 (31)	34	15 (44)	31	19 (61)	33	17 (52)	33	4 (12)
Baseline	29	9 (31)	34	15 (44)	31	19 (61)	33	14 (42)	33	5 (15)
FDA	29	11 (38)	34	15 (44)	31	21 (68)	33	15 (45)	33	7 (21)
Bazett	29	21 (72)	34	21 (62)	31	26 (84)	33	20 (61)	33	18 (55)
Increase ≥ 60 msec										
Fridericia	29	1 (3)	34	0 (0)	31	1 (3)	33	0 (0)	33	0 (0)
Baseline	29	1 (3)	34	0 (0)	31	1 (3)	33	0 (0)	33	0 (0)
FDA	29	1 (3)	34	1 (3)	31	1 (3)	33	0 (0)	33	0 (0)
Bazett	29	1 (3)	34	3 (9)	31	4 (13)	33	5 (15)	33	1 (3)
Treatment Period 2										
Increase ≥ 30 msec										
Fridericia	26	14 (54)	31	15 (48)	31	22 (71)	30	18 (60)	32	6 (19)
Baseline	26	13 (50)	31	15 (48)	31	22 (71)	30	19 (63)	32	6 (19)
FDA	26	14 (54)	31	13 (42)	31	22 (71)	30	19 (63)	32	7 (22)
Bazett	26	17 (65)	31	13 (42)	31	21 (68)	30	23 (77)	32	21 (66)
Increase ≥ 60 msec										
Fridericia	26	1 (4)	31	0 (0)	31	1 (3)	30	0 (0)	32	0 (0)
Baseline	26	1 (4)	31	0 (0)	31	1 (3)	30	0 (0)	32	0 (0)
FDA	26	1 (4)	31	0 (0)	31	0 (0)	30	0 (0)	32	0 (0)
Bazett	26	0 (0)	31	1 (3)	31	1 (3)	30	1 (3)	32	3 (9)
Treatment Period 3										
Increase ≥ 30 msec										
Fridericia	25	13 (52)	30	21 (70)	29	20 (69)	–	–	–	–
Baseline	25	14 (56)	30	20 (67)	29	19 (66)	–	–	–	–
FDA	25	14 (56)	30	20 (67)	29	19 (66)	–	–	–	–
Bazett	25	14 (56)	30	20 (67)	29	19 (66)	–	–	–	–
Increase ≥ 60 msec							–	–	–	–
Fridericia	25	1 (4)	30	3 (10)	29	0 (0)	–	–	–	–
Baseline	25	1 (4)	30	3 (10)	29	0 (0)	–	–	–	–
FDA	25	1 (4)	30	3 (10)	29	0 (0)	–	–	–	–
Bazett	25	2 (8)	30	5 (17)	29	1 (3)	–	–	–	–

N=number of patients; ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine
*T_{MAX}=estimated time of maximum concentration (ILO = 2-4 hours post-dose; ZIP = 5-7 hours post-dose; QUET = 1-2.5 hours post-dose).
Each patient is counted once within each steady state if he/she had at least one QTc increase ≥30 msec or ≥60 msec from baseline.

(Source: Ilo522-2328-legacy report: Table 9-3, page 63)

4.2.7.2.3 Additional Analyses

The primary analysis was in period 1 (no additional inhibitors). Additional analyses for periods 2 and 3 were performed and the results are presented in Table 7. In comparison to treatment period 1, the mean change from baseline in QTcF (Fridericia correction) at T_{max} was numerically higher in all treatment groups for treatment period 2 and in iloperidone groups for treatment period 3.

Table 7. Summary statistics of QTcF change (95% CI) from baseline to steady state at Tmax during Treatment Periods 1, 2, and 3 (Primary QTc population)

	Ilo 8 mg	Ilo 12 mg	Ilo 24 mg	Zip	Quet
Period 1					
Sample size	28	34	31	32	33
Baseline					
Raw mean ± SD	385.9 ± 16.4	386.5 ± 17.1	379.0 ± 14.7	383.4 ± 13.5	383.2 ± 18.9
Change in QTcF					
Raw mean ± SD	8.5 ± 10.5	9.0 ± 12.5	15.4 ± 11.7	9.6 ± 11.0	1.3 ± 11.1
LS mean*	9.1	9.7	14.6	9.7	1.3
(95% CI for LS mean)	(4.9, 13.3)	(5.8, 13.6)	(10.6, 18.9)	(5.7, 13.7)	(-2.5, 5.2)
Period 2					
Sample size	26	31	31	30	32
Baseline					
Raw mean ± SD	387.3 ± 16.1	386.1 ± 17.7	379.0 ± 14.7	383.0 ± 13.2	382.8 ± 19.1
Change in QTcF					
Raw mean ± SD	11.2 ± 12.0	11.6 ± 16.8	17.5 ± 10.3	15.9 ± 11.8	2.6 ± 11.5
LS mean	11.9	11.9	16.0	15.4	2.1
(95% CI for LS mean)	(7.2, 16.6)	(7.6, 16.3)	(11.7, 20.3)	(11.1, 19.8)	(-2.1, 6.3)
Period 3					
Sample size	25	30	29	--	--
Baseline				--	--
Raw mean ± SD	387.5 ± 16.4	384.5 ± 15.6	379.6 ± 14.9	--	--
Change in QTcF				--	--
Raw mean ± SD	15.7 ± 14.1	19.3 ± 17.1	19.5 ± 11.9	--	--
LS mean	15.8	18.5	17.6	--	--
(95% CI for LS mean)	(10.1, 21.6)	(13.2, 23.9)	(12.3, 22.9)	--	--

* The least square means and confidence intervals for Period 1 are provided by the reviewer. These results are slightly different than the results reported on Table 9.2.1-2, page 308 as the sponsor's results included two additional patients from the secondary QTc population)

(Source: Ilo522-2328-legacy report: Table 9-2, page 60, Table 9.2.1-2, pages 309-310)

Reviewer's Comments: The results produced by the sponsor were based on 2-sided 95% CI. We calculated 2-sided 90% CI for our analysis.

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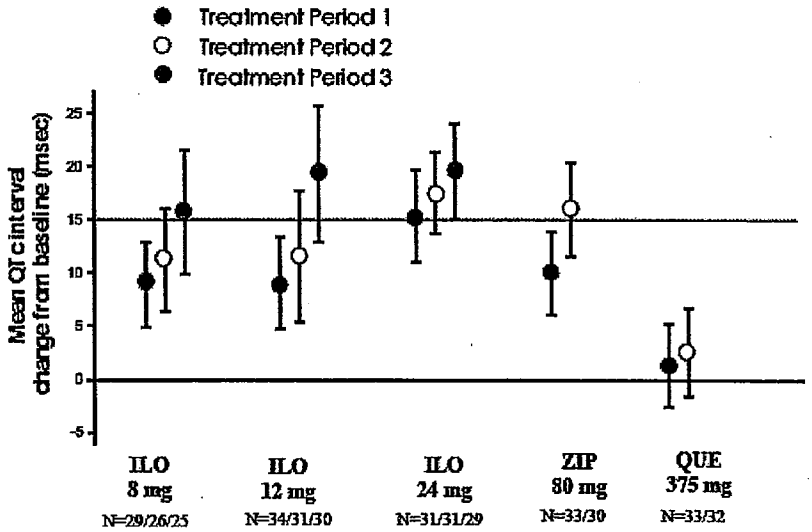
Figure 2: Mean QTcF Change from Baseline to Steady State T_{max} during Treatment Periods 1, 2, and 3



ILO=iloperidone; ZIP=ziprasidone; QUE=quetiapine
P1=Period 1, P2=Period 2, P3=Period 3
Note: * T_{MAX} = estimated time of maximum concentration (ILO=2-4 hours post-dose; ZIP=5-7 hours post-dose; QUET= 1-2.5 hours post-dose)
Source: Figure 9.2-1

(Source: Ilo522-2328-legacy report: Figure 9-2, page 61)

4.2.7.3 Safety Analysis

There were *no deaths* in this study.

- Three patients experienced a serious adverse event (SAEs) during treatment with study medication. One 38 yr old male randomized to the iloperidone 8 mg b.i.d. group experienced a run of severe supraventricular tachycardia (>200bpm) on day 7 which responded to cardizem. The patient was discontinued from study drug and switched to olanzapine. A 47 yr old female, randomized to iloperidone 24 mg q.d. experienced new onset uncontrolled DM 11 days after study drug. The other SAE was aggravated psychosis on quetiapine
- Additionally, one patient experienced a SAE (altered mental status and brief psychotic reaction) before randomization, and one patient experienced a SAE (pain in extremities and shortness of breath) after study medication (iloperidone 8 mg b.i.d.) was discontinued.
- There were nine discontinuations due to AEs (6 from the various iloperidone groups). A 49 yr old male randomized to ILO 12 mg b.i.d. experienced mild sinus bradycardia on Study Day 19 and moderate hypotension on Study Day 25. On Study Day 30 the patient experienced moderate presyncope and sinus bradycardia (60 and 58 bpm, morning and evening measurements respectively). The patient did not receive any further treatment for the sinus bradycardia and was withdrawn from the study. His pulse was within normal ranges by the following day. Another 43 yr old male

experienced ongoing intermittent tachycardia (reported as tachycardia NOS) on iloperidone 24 mg q.d. and was discontinued from study drug on day 27.

- 15 patients experienced cardiac AEs- of these 12 were from the iloperidone group. Ten were reported as tachycardia NOS. The other two events were supraventricular tachycardia and sinus bradycardia as described above.
- The most common (>10%) treatment-emergent AEs for iloperidone-treated patients included headache, anxiety, dyspepsia, insomnia, dizziness, constipation, tachycardia, diarrhea, EPS, fatigue, dry mouth, nasal congestion, somnolence, akathisia, cough, sedation, and pharyngitis.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

Average peak concentrations (average of concentrations on steady-state days 1 and 2) and mean peak concentration ratios in the presence vs. the absence of metabolic inhibitors are presented in Table 8.

- Compared with peak steady-state concentration of iloperidone in the absence of inhibition (Period 1), mean peak concentrations in the presence of paroxetine (Period 2) increased 29-64%, with the lowest percentage increase in the iloperidone 24 mg q.d. group and the highest in the iloperidone 8 mg b.i.d.
- The increases in the iloperidone concentrations in the presence of paroxetine and ketoconazole (Period 3) were 54-134%, with lowest percentage increase in the iloperidone 24 mg q.d. group and the highest in the iloperidone 8 mg b.i.d.
- For the primary active metabolite of iloperidone, P88, the corresponding increases in concentrations were comparable or slightly larger, i.e. 29-73% in Period 2, and 84-171% in Period 3.
- For iloperidone metabolite P95 (non-active), mean peak concentrations reduced to ~50% in Period 2 and to ~30% in Period 3, compared to the peak concentration levels without metabolic inhibition in Period 1. Mean peak concentration increases due to metabolic inhibitor ketoconazole were 24%, and 334% for ziprasidone, and quetiapine respectively.

Table 8: Average Peak Concentrations and Ratios of Average Peak Concentrations in the Presence and in the Absence of Metabolic Inhibitors

	Average Peak Concentration						Ratio			Ratio		
Analyte	Period 1[b]		Period 2[b]		Period 3[b]		(periods 2/1)			(periods 3/1)		
Iloperidone	Mean	CV[c]	Mean	CV	Mean	CV	Mean	N	CV	Mean	N	CV
Ilo 8 mg bid	12.35	57	19.00	53	25.62	42	1.64	25	30	2.34	24	33
Ilo 12 mg bid	20.88	43	32.20	44	47.43	55	1.60	31	41	2.29	30	43
Ilo 24 mg qd	29.47	39	36.01	56	46.56	41	1.29	29	62	1.54	26	38
P88												
Ilo 8 mg bid	18.03	52	28.77	36	44.92	32	1.73	25	35	2.71	24	39
Ilo 12 mg bid	24.44	37	36.84	28	54.55	38	1.57	31	25	2.31	30	32
Ilo 24 mg qd	33.12	45	39.77	40	60.10	50	1.29	29	37	1.84	27	39
P95												
Ilo 8 mg bid	33.39	62	15.15	48	11.01	67	0.50	25	41	0.35	24	62
Ilo 12 mg bid	47.22	53	20.83	48	15.89	89	0.52	31	49	0.31	30	50
Ilo 24 mg qd	54.59	50	20.43	58	14.44	103	0.43	29	78	0.25	27	78
Ziprasidone	168.27	43	211.91	41	-	-	1.33	28	47	-	-	-
Quetiapine	825.95	61	2146.8	39	-	-	4.34	31	110	-	-	-

Note: (a) Average of peak concentrations at steady-state day 1 and day 2. (b) Period 1: no inhibition, Period 2: add one inhibitor, and Period 3: add two inhibitors. (c) CV: coefficient of variation in %.

(Source: Ilo522-2328-legacy report: Table 9-4, page 65)

4.2.7.4.2 Exposure-Response Analysis

Linear models were used to assess the effects of concentrations on mean QTc change. The primary QTc variable in the analysis was the average QTc of three measurements obtained at the T_{max} (one on each of the three steady-state days during the treatment periods). The timing of the QTc measurements was compound-dependent as they were collected at the T_{max} for each compound. The QTcs measured at the corresponding timepoints during the three days prior to treatment were averaged similarly, and were defined as baseline QTcs. Mean QTc change was the difference between the mean QTc during treatment and the mean QTc at baseline.

Mean QTc change from baseline at T_{max} in each treatment period was the dependent variable. The independent variables included the corresponding mean QTc at baseline, and concentrations (parent and metabolites) at their T_{max}. Concentrations were centered at the sample mean in each treatment period, and scaled by ~ 1/2 standard deviation, i.e. 10 ng/mL for iloperidone and metabolites, 50 ng/mL for ziprasidone, and 500 ng/mL for quetiapine. Baseline mean QTc was centered at 385 ms and scaled by 10 ms. The parameters in the model were intercept, slope for baseline QTc term, and slope for concentration term. The intercept represented the average QTc change for a patient whose drug concentration was at the centered concentration value and whose baseline QTc was at 385 ms. The slope for the concentration term measured the concentration effect on QTc change. A positive slope indicated an increase in QTc change as concentration increased by the magnitude of the scaled concentration, e.g. 10 ng/mL for iloperidone, P88 and P95, 50 ng/mL for ziprasidone and 500 ng/mL for quetiapine. The slope of the QTc term was interpreted similarly as the effect on QTc change per 10 ms increase in the baseline QTc. Analyses were carried for each analyte in each treatment period.

The intercept and slopes (for both baseline QTc and peak concentration of the analyte) together with the centered sample mean concentrations are presented in Table 9.

The QTc change in the presence of inhibition (Periods 2 and 3) was larger, compare to the QTc change in the absence of inhibition (Period 1). Baseline QTc was an important factor in the change of QTc, and greater QTc baseline was associated with lower change in QTc. For iloperidone treated patients, a 10 ms increase in baseline QTc resulted in a 2-4 ms reduction in QTc change regardless the presence of metabolic inhibition. Within treatment period, QTc change tended to increase with concentrations of iloperidone and its metabolite P88 for iloperidone treated patients. The concentration effects were significant for iloperidone at Period 2 and for P88 at Period 2 and 3 ($p < 0.02$). For ziprasidone and quetiapine, larger QTc changes and higher drug concentrations were associated with metabolic inhibition. The effects of baseline QTc on QTc change was similar to that in the iloperidone treated patients. None of the concentration effect on QTc change within treatment period was significant ($p = 0.3861$).

Table 9: Modeling the Effect of Drug and Metabolites Concentrations on the Mean QTc Change at T_{max}

Analyte	Term	Period 1			Period 2			Period 3		
		Est	S.E.	p-val[b]	Est	S.E.	p-val	Est	S.E.	p-val
Ilo	Intercept[a]	11.34	1.44	<.0001	13.35	1.50	<.0001	18.66	1.64	<.0001
	Slope 1[a]	-2.17	0.87	.0148	-3.70	0.91	<.0001	-2.78	1.04	.0089
	Slope 2[a]	1.66	1.30	.2059	2.54	0.91	.0063	1.30	0.74	.0845
	C_{MEAN}[a]	21.00			29.59			40.00		
	N[a]	91			88			84		
P88	Intercept	10.42	1.42	<.0001	13.14	1.38	<.0001	17.76	1.52	<.0001
	Slope 1	-3.48	0.88	.0001	-3.34	0.83	.0001	-2.91	0.98	.0041
	Slope 2	1.39	1.16	.2312	2.64	1.05	.0135	2.63	0.68	.0002
	C_{MEAN}	25.23			36.23			54.65		
	N	91			88			84		
P95	Intercept	10.40	1.43	<.0001	13.12	1.43	<.0001	17.63	1.65	<.0001
	Slope 1	-3.68	0.85	<.0001	-3.75	0.84	<.0001	-4.21	1.00	<.0001
	Slope 2	0.54	0.56	.3340	1.30	1.39	.3530	1.03	1.28	.4251
	C_{MEAN}	45.31			19.14			14.10		
	N	91			88			84		
Zip	Intercept	6.50	1.76	.0009	14.29	2.26	<.0001	-	-	-
	Slope 1	-2.27	1.36	.1052	-2.53	1.71	.1505	-	-	-
	Slope 2	-0.04	1.27	.9758	0.79	1.15	.4982	-	-	-
	C_{MEAN}	168			198					
	N	33			30					
Que	Intercept	1.72	2.05	.4093	3.37	2.39	.1705	-	-	-
	Slope 1	-2.39	1.05	.0301	-3.37	1.19	.0084	-	-	-
	Slope 2	1.79	2.03	.3861	1.21	1.44	.4051	-	-	-
	C_{MEAN}	826			2147					
	N	33			31					

Note: (a) The units for Intercept is msec. The unit of Slope 1 (the slope of the baseline QTc term) is msec/(10 msec of baseline QTc). The units of Slope 2 (the slope of the analyte concentration term)) are msec/(10 ng/mL) for iloperidone and its metabolites, msec/(50 ng/mL) for ziprasidone, and msec/(500 ng/mL) for quetiapine. C_{MEAN} is the centered mean concentration in the treatment period. N: number of patients. (b) p-values were based on Wald's test and referred to the null hypothesis that the term equals zero.

(Source: Ilo522-2328-legacy report: Table 9-5, page 67)

Reviewer's Comments: The effect of iloperidone and its metabolites on QTc appears to be concentration dependent. The exposure-response analysis by the sponsor was not thoroughly reviewed. The reviewer's also did not conduct exposure-response analyses for iloperidone due to assay sensitivity issues (see clinical pharmacology reviewer's analyses)

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

This study was not a placebo-controlled study. Active therapies (ziprasidone and quetiapine) were used as references. However, no direct comparison between iloperidone and ziprasidone/quetiapine was performed. The drugs were also administered open-label. Thus, the study is subject to potential bias.

In the sponsor's primary analysis, the baseline QTc measurements were averaged over three baseline days around the T_{max} and the endpoint QTc measurements were averaged over three steady-state days around the T_{max}. Because the study was not designed for a time-matched analysis, the following analysis is only to mimic the E-14 analysis. The endpoint QTc measurements were the 9 measurements taken over 9 time points on Steady-State Day 3. The baseline QTc measurements were the 9 measurements taken over 9 time points on Baseline Day 0. At each timepoint, an ANCOVA model was utilized with gender and treatment group as factors and an adjusted baseline QTc measurement as a covariate. The adjusted baseline was computed by subtracting the average baseline from each patient's baseline measurement.

For iloperidone 12 mg, iloperidone 24 mg, and quetiapine, the largest effect on the QTcF occurs in the morning. For iloperidone 8 mg and ziprasidone, the largest effect occurs in the afternoon and late afternoon.

These results along with the primary results suggest that iloperidone (8 mg – 24 mg) is associated with a prolongation of the QT interval above the threshold established by the ICH-E14 guidance.

Table 10. Time-matched analysis of QTc (Fridericia correction) change (90% CI) from baseline (Day 0) to steady state (Day SSD3) during Treatment Period 1 (Primary QTc population)

	Ilo 8 mg	Ilo 12 mg	Ilo 24 mg	Zip	Quet
sample size	28	34	31	32	33
Time 1	10.1 (4.8, 15.4)	9.0 (4.0, 14.0)	14.7 (9.6, 19.8)	6.0 (0.9, 11.1)	3.5 (-1.5, 8.5)
Time 2	8.9 (3.2, 14.6)	8.2 (3.0, 13.4)	16.8 (11.4, 22.2)	7.6 (2.2, 13.0)	5.1 (-0.2, 10.4)
Time 3	6.6 (1.5, 11.7)	11.8 (7.1, 16.5)	14.1 (9.1, 19.1)	8.8 (4.0, 13.6)	2.2 (-2.6, 7.0)
Time 4	11.1 (6.0, 16.2)	7.1 (2.4, 11.8)	10.8 (5.9, 15.7)	6.1 (1.2, 11.0)	0.2 (-4.6, 5.0)
Time 5	10.5 (5.0, 16.0)	7.8 (2.9, 12.7)	6.6 (1.5, 11.7)	6.9 (1.8, 12.0)	-0.8 (-5.8, 4.2)
Time 6	6.3 (1.4, 11.2)	8.5 (4.1, 12.9)	7.6 (3.0, 12.2)	12.9 (8.3, 17.5)	5.2 (0.7, 9.7)
Time 7	8.5 (4.0, 13.0)	7.5 (3.4, 11.6)	3.9 (-0.3, 8.1)	11.6 (7.4, 15.8)	-1.3 (-5.4, 2.8)
Time 8	5.5 (0.6, 10.4)	8.5 (4.1, 12.9)	5.0 (0.4, 9.6)	3.6 (-1.0, 8.2)	-0.6 (-5.1, 3.9)
Time 9	5.2 (0.0, 10.4)	7.1 (2.3, 11.9)	2.5 (-2.4, 7.4)	4.4 (-0.5, 9.3)	-1.2 (-6.0, 3.6)

(Source: Reviewer's results)

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

5.2.1 Assay Sensitivity

Using the quetiapine as the positive control, assay sensitivity could not be established. Based on the exposure-response analysis from TQT studies submitted to [redacted] and NDA 21999 for paliperidone, quetiapine is expected to prolong QTc ~10 ms at mean concentration of 1000 ng/mL. In this study, quetiapine exposures in period 1 (mean C_{max} 825 ng/mL) and period 2 (mean C_{max} 2146 ng/mL) are expected to exhibit QTc prolongation ~10 ms. However, none of the periods resulted in such effects on QTc (see Figure 3).

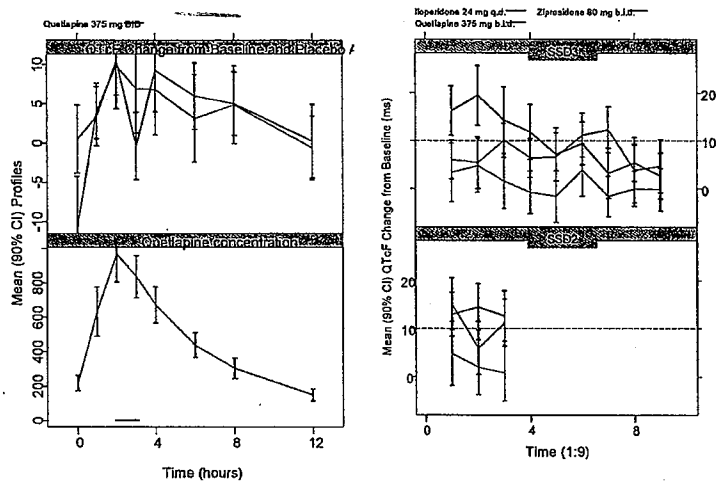
Additionally, the time-course of ΔQTc closely followed plasma quetiapine concentration-time profile in [redacted] and paliperidone studies. No such time course was seen on any of the days in the current study. Figure 3 shows time course of change in QTc from baseline on days SSD2 and SSD3. Note that there were no pharmacokinetic samples available on SSD3. There are two possible reasons for such behavior in QT studies (1) absence of assay sensitivity due to poor study conduct or (2) inability to correct for placebo effect as the study did not include concurrent placebo arm.

Due to inherent limitation in study design, limited data were available for exposure response analyses. From quetiapine treated group, only 130 time matched concentration-ΔQTcF observations were available. Given the absence of placebo data and lack of time course in effect on QTc, the decision was made no to conduct exposure response analyses for quetiapine.

Figure 3: Mean ΔΔQTcF (upper panel) and quetiapine (bottom panel) concentration-time profile from [redacted] and paliperidone studies. ΔQTcF-time profiles from iloperidone study on SSD3 (top panel) and SSD2 (bottom panel)

[redacted] QT study | Paliperidone (NDA 21999) QT study | Iloperidone QT study

b(4)



(Source: Reviewer's results)

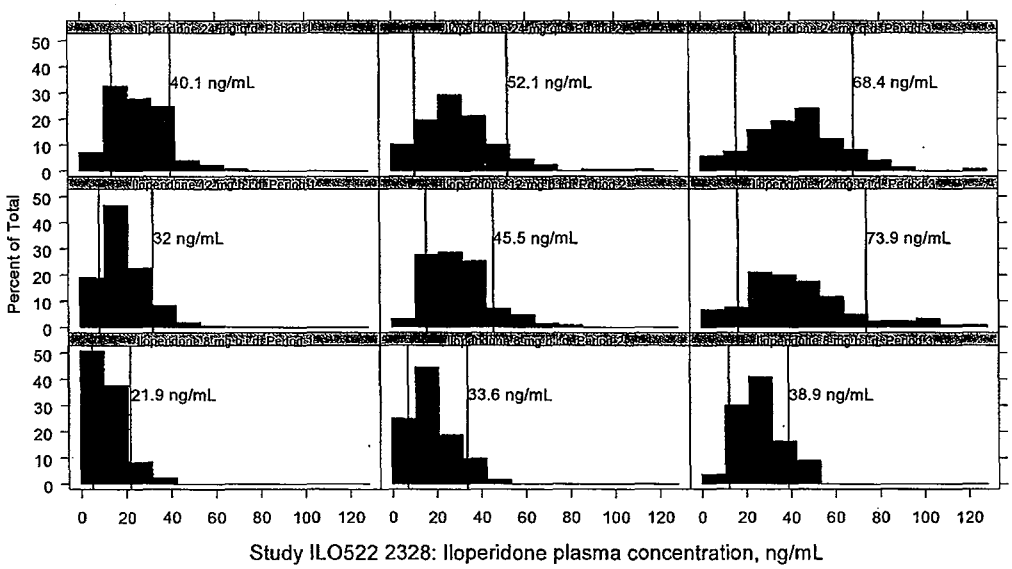
5.2.2 Exposure-Response Analyses for Iloperidone

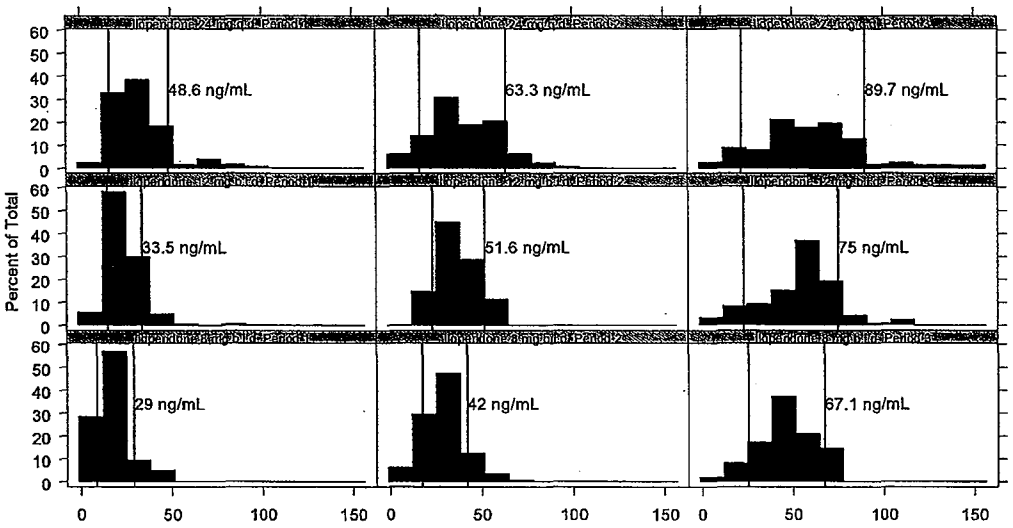
Since the assay sensitivity cannot be established, the reviewer did not conduct exposure-response analyses for iloperidone.

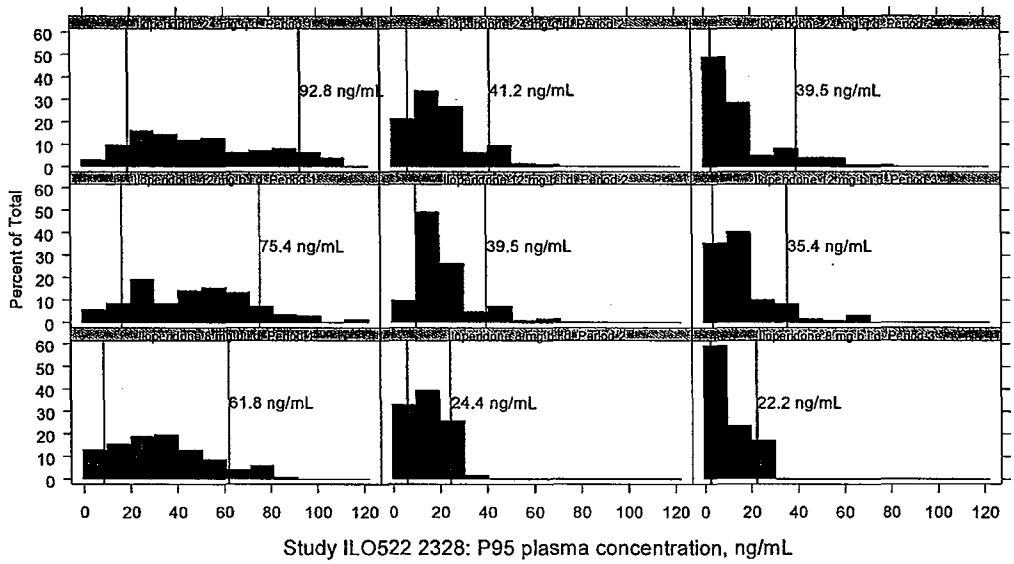
5.2.3 Dose Evaluation

Pharmacokinetic data were available from study VP-VYV-683-3101, a randomized, double-blind, placebo- and ziprasidone-controlled, multi-center clinical trial to evaluate the efficacy, safety and tolerability of a 24 mg/day dose iloperidone given b.i.d. for 28 days to schizophrenic patients in acute exacerbation followed by a long-term treatment phase. The short-term double-blind phase consisted of a 7-day fixed titration period followed by a 21-day dosing period. Iloperidone was provided as an over-encapsulated tablet containing 1, 2, 4, 6, 8, 10, or 12 mg. Blood samples for analysis of plasma concentrations of iloperidone were collected on Days 7, 14, 21 and 28 (or at the time of premature discontinuation). Figure 1 illustrates distribution of iloperidone, P88 and P95 concentration in VP-VYU-683-3101. The observed 90th percentiles were 27.3, 40.6 and 60.8 ng/mL, respectively. Figure 4 illustrates distribution of iloperidone, P88 and P95 concentration in ILO522 2328. The concentrations achieved in the QT study reasonably cover therapeutic concentration range at 24mg/day (12mg BID) clinical dose or lower.

Figure 4: Distribution of Iloperidone, P88 and P95 concentrations in ILO522 2328 after 3 doses. The vertical line represent 10th and 90th percentile. The number corresponds to the 90th percentile concentration.







5.3 CLINICAL ASSESSMENTS

None of the clinical events identified to be of particular importance per the ICH E14 guidelines (i.e. death, seizures, syncope and significant ventricular arrhythmias) were reported in this study. However, one patient experienced sinus bradycardia and presyncope. Another patient had supraventricular tachycardia reported as a SAE. Tachycardia NOS occurred more frequently in the iloperidone treatment groups.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Iloperidone efficacy has been established in the dose range of 4-24 mg/day. The recommended target dosage of iloperidone is 12 mg/day administered BID. The recommended titration schedule to target dose is 1, 2, 4, 6 mg BID on days 1, 2, 3, and 4 respectively. After reaching the target 12 mg/day dose, titration to the maximum daily dose of 12 mg BID (24 mg/day) should occur over a 3-day period.	
Maximum tolerated dose	Healthy volunteers: 3 mg (ILPB101) No MTD studies were performed in patients with schizophrenia. It is believed that the MTD has not been reached when up to 32 mg/d was administered to patients with schizophrenia (ILPB203).	
Principal adverse events	In healthy volunteers, the AEs that lead to the declaration of the MTD were the following: dysphoria, dizziness, hypotension, tachycardia, lethargy, nausea and drowsiness (ILPB101)	
Maximum dose tested	Single Dose	Without PK: 32 mg (ILPB203) With PK: 24 mg QD (ILO522 2328)
	Multiple Dose	12 mg BID (ILO522 0112)
Exposures Achieved at Maximum Tested Dose	Single Dose	mean (%CV) C_{max}: 29.47 (39) ng/mL (ILO522 2328) AUC: not determined
	Multiple Dose	mean (%CV) C_{max}: 32.14 (43) ng/mL (ILO522 0112) AUC_τ: 231.9 (48) ng*hr/mL
Range of linear PK	Iloperidone and its metabolites, P88 and P95, show dose proportionality at steady-state in patients with schizophrenia over the dose range of 2 to 12 mg BID. (ILO522 0112).	
Accumulation at steady state	Considering that C_{max} of iloperidone after a single dose of 3 mg was in the order of 3 ng/mL, the steady-state C_{max} of iloperidone at the 12 mg BID dose was 32.14 ng/mL (ILO522 0112), and assuming dose-proportionality, accumulation of iloperidone with multiple BID dosing appears to be at least two-fold.	
Metabolites	There are two major iloperidone metabolites: • P88 – has similar receptor binding profile as iloperidone and crosses the blood-brain barrier • P95 – has different receptor binding profile as iloperidone and does not cross the blood-brain barrier, therefore considered "centrally" inactive	
Absorption	Absolute/Relative Bioavailability	Iloperidone absorption was at least 56% of a 3 mg [^{14}C]iloperidone dose given to normal healthy volunteers (ILO522 2301).

		An absolute bioavailability (BA) study was not performed. Absolute bioavailability is roughly estimated to be about 36% in CYP2D6 extensive metabolizers (EM) and about 54% in CYP2D6 poor metabolizers (PM), which is compatible with first-pass effect being smaller in PM due to lower CYP2D6 activity (ILO522 2301).
	Tmax	• Iloperidone: 1.5-1.8 (0.75-8.0) h • P88: 2.5-3.0 (0.75-8.0) h • P95: 2.5-2.8 (1-12) h (ILO522 0112)
Distribution	Vd/F or Vd	V_d/F (ILO522 2301) • 2000 L in CYP2D6 extensive metabolizers (EM) • 1310 L in CYP2D6 poor metabolizers (PM)
	% bound	Plasma protein binding of iloperidone is about 95% and is similar in man and in laboratory animals. Protein binding was unchanged in subjects with renal impairment (ILO522 0102), hepatic impairment (ILO522 0103) and in the presence of ketoconazole in blood (ILO522 0107).
Elimination	Route	The main route of elimination in humans is urine (70% of the dose in CYP2D6 extensive metabolizers (EM), 61% in CYP2D6 poor metabolizers (PM)), with biliary excretion to feces contributing a minor portion (21% in CYP2D6 EM, 25% in CYP2D6 PM). (ILO522 2301)
	Terminal t½	• Iloperidone: 19.0/19.5 h (EM/PM) • P88: 23.2/12.7 h (EM/PM) • P95: 25.8/23.0 h (EM/PM) (ILO522 2301)
	CL/F or CL	CL/F (ILO522 2301) • 102 L/h in CYP2D6 extensive metabolizers (EM) • 47.7 L/h in CYP2D6 poor metabolizers (PM)
Intrinsic Factors	Age	No specific study was conducted to evaluate the effect of age. In the Phase 2 efficacy and safety study ILP2001,

		plasma iloperidone concentrations predicted from a PK model were found not to correlate with age. Similarly, in the population PK analysis of another study (VP-VYY-683-3101-PK01), there was no indication that age affected PK characteristics of iloperidone or its metabolites P88 and P95.
	Sex	Having adjusted for body size, exposure AUC for each of iloperidone, P88, and P95 is 48% larger in women than in men (VP-VYY-683-3101-PK01). The practical importance of this finding is uncertain, as there is no evidence that women have more tolerability or safety problems than men when receiving recommended doses of iloperidone (Integrated Summary of Safety).
	Race	No specific study was conducted to evaluate the effect of race or ethnic origin. In population PK analysis, no correlation was found between race (Caucasian, African-American, Asian, other) and plasma exposure (VP-VYY-683-3101-PK01).
	Hepatic & Renal Impairment	Hepatic Impairment (HI) (ILO522 0103) Iloperidone: - C_{max} (ng/mL) with (%CV) o Normal: 1.75 (56) o HI: 1.68 (40) o % change: -4% - $AUC_{0-\infty}$ (ng*hr/mL) with (%CV) o Normal: 22.0 (36) o HI: 26.2 (38) o % change: 19% P88: - C_{max} (ng/mL) with (%CV) o Normal: 1.02 (63) o HI: 1.74 (21) o % change: 71% - $AUC_{0-\infty}$ (ng*hr/mL) with (%CV) o Normal: 32.3 (53) o HI: 47.8 (40) o % change: 48% P95: - C_{max} (ng/mL) with (%CV)

		o Normal: 1.90 (32) o HI: 1.54 (70) o % change: -19% - $AUC_{0-\infty}$ (ng*hr/mL) with (%CV) o Normal: 71.5 (39) o HI: 68.1 (32) o % change: 5% <u>Renal Impairment (RI)</u> (ILO522 0102) Iloperidone: - C_{max} (ng/mL) with (%CV) o Normal: 2.2 (35) o RI: 2.3 (71) o % change: 5% - $AUC_{0-\infty}$ (ng*hr/mL) with (%CV) o Normal: 26.6 (23) o RI: 47.9 (82) o % change: 80% P88: - C_{max} (ng/mL) with (%CV) o Normal: 2.01 (38) o RI: 2.00 (39) o % change: -0.5% - $AUC_{0-\infty}$ (ng*hr/mL) with (%CV) o Normal: 62.5 (62) o RI: 44.9 (40) o % change: -28% P95: - C_{max} (ng/mL) with (%CV) o Normal: 4.2 (58) o RI: 3.9 (54) o % change: -7% - $AUC_{0-\infty}$ (ng*hr/mL) with (%CV) o Normal: 141.2 (48) o RI: 447.4 (61) o % change: 217%
Extrinsic Factors	Drug interactions	<u>Dextromethorphan</u> (ILO522 0104) Iloperidone: - C_{max} (ng/mL) with (%CV) o ILO: 2.79 (27) o ILO+DEX: 2.75 (30) o % change: -1% - $AUC_{0-\infty}$ (ng*hr/mL) with (%CV) o ILO: 29.4 (36) o ILO+DEX: 30.2 (40) o % change: 3%

		o ILO+KETO: 160.4 (44) o % change: 38% Fluoxetine (ILO522 0108) Iloperidone: - C_{max} (ng/mL) with (%CV) o ILO: 2.49 (31) o ILO+FLUOX: 4.22 (34) o % change: 41% - $AUC_{0-\infty}$ (ng*hr/mL) with (%CV) o ILO: 27.1 (29) o ILO+FLUOX: 62.7 (23) o % change: 131% P88: - C_{max} (ng/mL) with (%CV) o ILO: 2.67 (27) o ILO+FLUOX: 4.39 (28) o % change: 64% - $AUC_{0-\infty}$ (ng*hr/mL) with (%CV) o ILO: 54.2 (28) o ILO+FLUOX: 118.7 (28) o % change: 119% P95: - C_{max} (ng/mL) with (%CV) o ILO: 4.10 (42) o ILO+FLUOX: 1.21 (23) o % change: -70% - $AUC_{0-\infty}$ (ng*hr/mL) with (%CV) o ILO: 127.1 (31) o ILO+FLUOX: 59.2 (29) o % change: -53%
	Food Effects	No statistically significant differences were observed in the rate and extent of exposure (C_{max} and $AUC_{0-\infty}$) of iloperidone, P88, or P95 when iloperidone was administered as a tablet under fasted or fed conditions. (ILO522 0105) Iloperidone: - C_{max} (ng/mL) o Fasted: 3.3 ± 1.5 o High Fat: 2.8 ± 0.8 o % change: -15% - $AUC_{0-\infty}$ (ng*hr/mL) o Fasted: 44.4 ± 19.7

		o High Fat: 47.5 ± 19.1 o % change: 7% P88: - C_{max} (ng/mL) o Fasted: 2.9 ± 0.8 o High Fat: 2.7 ± 0.8 o % change: -7% - $AUC_{0-\infty}$ (ng*hr/mL) o Fasted: 71.8 ± 24.4 o High Fat: 74.5 ± 21.2 o % change: 4% P95: - C_{max} (ng/mL) o Fasted: 3.6 ± 1.8 o High Fat: 2.9 ± 1.4 o % change: -19% - $AUC_{0-\infty}$ (ng*hr/mL) o Fasted: 130.9 ± 52.1 o High Fat: 121.7 ± 48.2 o % change: 7%
Expected High Clinical Exposure Scenario	The maximum recommended human dose (MRHD) is 24 mg/day administered as 12 mg BID. In the thorough QT study (ILO522 2328), the average peak concentrations of iloperidone 24 mg QD in the absence and presence of the CYP2D6 inhibitor paroxetine (20 mg QD) and the CYP3A4 inhibitor ketoconazole (200 mg BID) was investigated. Iloperidone: - C_{max} (ng/mL) with (%CV) o No inhibitors: 29.47 (39) o With inhibitors: 46.56 (41) o % change: 58% P88: - C_{max} (ng/mL) o No inhibitors: 33.12 (45) o With inhibitors: 60.10 (50) o % change: 81% P95: - C_{max} (ng/mL) o No inhibitors: 54.59 (50) o With inhibitors: 14.44 (103) o % change: -74%	

6.2 TABLE OF STUDY ASSESSMENTS

Table 3-7 Assessment schedule (Pre-treatment phase)

	Phase	Pre-Treatment					
	Period	Screen	Taper[a]	Wash-out and Baseline			
Evaluations	Day	-30 to –12	-11 to -5	-4 to -3	-2	-1	0
Informed consent		X					
Relevant medical history / Current medical condition(s)		X	X	X	X	X	X
Prior and current medications		X	X	X	X	X	X
Prior psychotropic medication(s)		X	X				
Screened Subject Log, Demography, DSM-IV diagnosis, Pharmacogenetics		X					
Meal Record					X	X	X
Inclusion/exclusion criteria		X		X			
Vital signs		X			Twice daily		
Electrocardiogram		X			XXX	XXX	XXXXXXXXX
Laboratory evaluation		X[b,c]					X[d]
Physical examination		X					X[d]
IVRS call		X[e]			X[e]		
Urine drug screen		X					X[d]
Clinical Global Impression of Severity (CGI-S) score, Pregnancy test		X					X
Adverse events (serious events [SAEs] only)		X	X	X	X	X	X

[a] This Taper Period occurred in an outpatient setting. If deemed necessary by the investigator, certain patients could undergo the Taper Period in an inpatient setting.

[b] Laboratory assessments could be repeated to confirm an abnormal finding for purposes of meeting inclusion/exclusion criteria.

[c] In addition to routine laboratory evaluations, hepatitis A and B and Thyroid Stimulating Hormone (TSH) tests were performed for screening purposes.

[d] Repeated at baseline only if the screening evaluations were performed more than 14 days before Day 0.

[e] IVRS was notified of the patient identification number at the screening visit. On Day -2, patients were randomized to treatment using IVRS. IVRS was also called to report patient completion or discontinuation.

Table 3-8 Assessment schedule (Treatment phase)

Phase		Treatment phase												
Period		Treatment Period 1[a]				Treatment Period 2[b]				Treatment Period 3[c] (Iloperidone treated patients only)				
Evaluations	Day	D1 to DY[d]	SSD1	SSD2	SSD3	DX[e]-DY[d]	SSD1	SSD2	SSD3	DX[e]-DY[d]	SSD1	SSD2	SSD3	SC[f]
Meal Record			X	X	X		X	X	X		X	X	X	
Vital signs		Twice daily												X
Electrocardiogram		X[g]	XXX	XXX	XXXXXXXX X	X[g]	XXX	XXX	XXX	X[g]	XXX	XXX	XXX	X
Laboratory evaluation, Physical exam, CGI-S														X
IVRS call														X[h]
Pharmacokinetic (PK) sample			X[i]	X[i]			X[i]	X[i]			X[j]	X[j]		
Pregnancy test, urine drug screen														X
Concomitant medications		Daily	X	X	X	X	X	X	X	X	X	X	X	X
Drug administration record (DAR)		Daily	X	X	X	X	X	X	X	X	X	X	X	X[k]
Adverse events (AEs), serious AEs (SAEs)		Daily	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion (SC) form														X

[a] SSD1, 2, and 3 were the following study days for: ILO LOW=13,14,15; ILO HIGH=15, 16, 17; ILO QD=16, 17, 18; RIS=11, 12, 13; ZIP=8, 9, 10; QUET=10, 11, 12.

[b] Patients received one metabolic inhibitor in addition to the assigned treatment during this period: iloperidone- and (prior to Amendment 2; see Section 4.1) risperidone-treated patients received paroxetine 20 mg q.d., and ziprasidone- and quetiapine-treated patients received ketoconazole 200 mg b.i.d. Note: Based on Amendment 2 (see Section 4.1).), the PM dose of ketoconazole was not given on the last day of study drug administration. SSD1, 2, and 3 are the following study days for: ILO LOW=21, 22, 23; ILO HIGH=23, 24, 25; ILO QD=24, 25, 26; RIS=19, 20, 21; ZIP=13, 14, 15; QUET=15, 16, 17.

[c] In addition to paroxetine; patients randomized to iloperidone received ketoconazole 200 mg b.i.d. during this period. Patients randomized to any other treatment did NOT enter this period. During this period, SSD1, 2, and 3 were the following study days for: ILO LOW=26, 27, 28; ILO HIGH=28; 29, 30; ILO QD = 29, 30, 31.

[d] Day Y (DY) is the day immediately prior to SSD1 of this period. The corresponding study day is dependent on treatment assignment (see Tables 3-3 and 3-4).

[e] Day X (DX) is the day immediately following SSD3 of the prior period. The corresponding study day is dependent on treatment assignment (see Tables 3-3 and 3-4).

[f] SC=study completion evaluation conducted the morning following SSD3 of Period 2 or 3, depending on treatment assignment, or at premature discontinuation. Quetiapine, ziprasidone, and risperidone-treated patients had study completion evaluations performed the morning following SSD3 of Period 2. Iloperidone-treated patients had study completion performed the morning following SSD3 of period 3.

[g] One ECG was performed on the second day of each period (ILO HIGH=Days 2, 19, and 27; ILO LOW=Days 2, 17; 25; ILO QD=Days 2, 20, 28; and RIS=Days 2, 15; ZIP=Days 2, 12; QUET=Days 2, 14)

[h] The IVRS was called to report patient completion or discontinuation.

[i] 3 blood samples drawn from patients in the ILO group, 2 from patients in the ZIP, QUET, and (prior to Amendment 2; see Section 4.1) RIS groups.

[j] Three blood samples for pharmacokinetic analysis were drawn from patients in the iloperidone group.

[k] Performed only at premature discontinuation.

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/s/

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