

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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

Table of Contents

1	EXECUTIVE SUMMARY.....	5
1.1	RECOMMENDATION ON REGULATORY ACTION	5
1.1.1	Risk Management Activity	5
1.1.2	Required Phase 4 Commitments	5
1.1.3	Other Phase 4 Requests.....	5
1.2	SUMMARY OF CLINICAL FINDINGS	5
1.2.1	Brief Overview of Clinical Program.....	5
1.2.2	Efficacy.....	6
1.2.3	Safety	6
1.2.4	Dosing Regimen and Administration.....	7
1.2.5	Drug-Drug Interactions.....	7
1.2.6	Special Populations.....	7
2	INTRODUCTION AND BACKGROUND.....	7
2.1	PRODUCT INFORMATION	7
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	8
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	8
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	8
2.5	PRESUBMISSION REGULATORY ACTIVITY	8
2.6	OTHER RELEVANT BACKGROUND INFORMATION.....	12
3	SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	12
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	12
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY	12
3.3	STATISTICAL REVIEW AND EVALUATION	12
3.4	DSI CLINICAL SITE INSPECTIONS	12
4	DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY.....	15
4.1	SOURCES OF CLINICAL DATA	15
4.2	TABLES OF CLINICAL STUDIES	15
4.3	REVIEW STRATEGY	19
4.4	DATA QUALITY AND INTEGRITY	20
4.5	COMPLIANCE WITH GOOD CLINICAL PRACTICES.....	21
4.6	FINANCIAL DISCLOSURES.....	21
5	CLINICAL PHARMACOLOGY	23
5.1	PHARMACOKINETICS	23
5.2	PHARMACODYNAMICS.....	24
5.3	EXPOSURE-RESPONSE RELATIONSHIPS	26
6	INTEGRATED REVIEW OF EFFICACY	26
6.1	INDICATION	26
6.1.1	Methods	26
6.1.2	General Discussion of Endpoints.....	26
6.1.3	Study Design.....	26
6.1.4	Efficacy Findings.....	27
6.1.5	Clinical Microbiology.....	31
6.1.6	Efficacy Conclusions.....	31
7	INTEGRATED REVIEW OF SAFETY	31

7.1	METHODS AND FINDINGS	31
7.1.1	Deaths	32
7.1.2	Other Serious Adverse Events	43
7.1.3	Dropouts and Other Significant Adverse Events	53
7.1.4	Other Search Strategies.....	60
7.1.5	Common Adverse Events	61
7.1.6	Less Common Adverse Events	65
7.1.7	Laboratory Findings.....	65
7.1.8	Vital Signs	70
7.1.9	Electrocardiograms (ECGs).....	73
7.1.10	Immunogenicity	75
7.1.11	Human Carcinogenicity	75
7.1.12	Special Safety Studies.....	75
7.1.13	Withdrawal Phenomena and/or Abuse Potential.....	76
7.1.14	Human Reproduction and Pregnancy Data	76
7.1.15	Assessment of Effect on Growth.....	76
7.1.16	Overdose Experience	76
7.1.17	Postmarketing Experience.....	77
7.2	ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	77
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	77
7.2.2	Description of Secondary Clinical Data Sources Used to Evaluate Safety.....	81
7.2.3	Adequacy of Overall Clinical Experience	81
7.2.4	Adequacy of Routine Clinical Testing.....	81
7.2.5	Adequacy of Metabolic, Clearance, and Interaction Workup.....	82
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.....	82
7.2.7	Assessment of Quality and Completeness of Data	82
7.2.8	Additional Submissions, Including Safety Update	83
7.3	SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	83
7.4	GENERAL METHODOLOGY	85
7.4.1	Pooling Data across Studies to Estimate and Compare Incidence.....	85
7.4.2	Explorations for Predictive Factors	85
7.4.3	Causality Determination	85
8	ADDITIONAL CLINICAL ISSUES.....	86
8.1	DOSING REGIMEN AND ADMINISTRATION	86
8.2	DRUG-DRUG INTERACTIONS	86
8.3	SPECIAL POPULATIONS.....	86
8.4	PEDIATRICS	86
8.5	ADVISORY COMMITTEE MEETING.....	87
8.6	LITERATURE REVIEW	87
8.7	POSTMARKETING RISK MANAGEMENT PLAN	87
8.8	OTHER RELEVANT MATERIALS	87
9	OVERALL ASSESSMENT.....	87
9.1	CONCLUSIONS	87
9.2	RECOMMENDATION ON REGULATORY ACTION	88
9.3	RECOMMENDATION ON POSTMARKETING ACTIONS	88
9.3.1	Risk Management Activity	88
9.3.2	Required Phase 4 Commitments.....	88

Clinical Review
Michelle M. Chuen, M.D.
NDA #22-192
Iloperidone

9.3.3	Other Phase 4 Requests.....	89
9.4	LABELING REVIEW.....	89
9.5	COMMENTS TO APPLICANT.....	89
10	APPENDICES.....	93
10.1	REVIEW OF INDIVIDUAL STUDY REPORTS.....	93
10.2	LINE-BY-LINE LABELING REVIEW.....	130
10.3	APPENDIX TO INDIVIDUAL STUDY REPORTS.....	131
10.4	APPENDIX TO DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY (SECTION 4).....	177
10.5	APPENDIX TO INTEGRATED REVIEW OF SAFETY (SECTION 7).....	180

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 ILPB202¹] 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.

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 piperidiny-benzisoxazole derivatives and has high (nM) affinity for 5HT_{2A}/NE_{α1}/NE_{α2c}/D₂/D₃/5HT_{1A} receptors in humans and acts as an antagonist at selected dopaminergic, serotonergic, 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 schizophrenia² 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.

- 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 their 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 subgroup 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 _____ who had some concerns regarding the sponsor's data integrity. Dianne Tesch, DSI Consumer Safety Officer, contacted _____ Per Ms. Tesch's 5/13/08 email, _____ had nothing specific regarding any of the sponsor's study sites. _____, and _____ impression was that the sponsor would stop at nothing to get approval. However, _____ had no hard evidence or promising leads.

b(6)

Clinical Review
 Michelle M. Chuen, M.D.
 NDA #22-192
 Iloperidone

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 source 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 ILPB202³] 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 ¹⁴ C-iloperidone following oral administration of 3 mg of iloperidone labeled with ¹⁴ C in 3 healthy adult subjects
ILO5222301	Open-label study to evaluate the absorption, distribution, metabolism and excretion of ¹⁴ C-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 disclosure⁴:

_____ 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 _____ and _____ 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 _____; site contributed _____ of the 671 ITT patients in the study.

_____ the principal investigator at Study Site _____, disclosed that _____ received honoraria for speaking activities. It is unlikely that these arrangements biased the study results since this was a _____ trial and _____ site contributed _____ 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 3005⁵, 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-∞} 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.

APPEARS THIS WAY ON ORIGINAL

TABLE 6.1.4.1: TREATMENT EFFECT SIZE AS EXPRESSED BY PANNS TOTAL SCORE, MEAN CHANGE FROM BASELINE AT ENDPOINT⁶ (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.

APPEARS THIS WAY ON ORIGINAL

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
BPRS	OC	NP	NP	NP	NP	NP	NA	NA	NA	NA	NA	ns	tr	NP	NP	NA
	LOCF	NA	NA	NA	NA	NA	NA	**	*	**	**	NA	NA	NA	NA	NA
	OC	NA	NA	NA	NA	NA	NP	NP	**	*	**	NA	NA	NA	NA	NA

Codes: ns= not significant (p>0.10)
 tr= trend (0.05<p≤0.10)
 * = significant (0.01<p≤0.05)
 **= highly significant (p≤0.01)
 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 ILPB202¹¹] 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.

APPEARS THIS WAY ON ORIGINAL

Clinical Review
 Michelle M. Chuen, M.D.
 NDA #22-192
 Iloperidone

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	<u>SUICIDE</u> 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	<u>CARDIAC FAILURE</u> 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	<u>SUICIDE</u> 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).

Clinical Review
 Michelle M. Chuen, M.D.
 NDA #22-192
 Iloperidone

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	<p><u>SUICIDE</u></p> <p>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.</p>

Clinical Review
 Michelle M. Chuen, M.D.
 NDA #22-192
 Iloperidone

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	<p><u>SUDDEN DEATH</u></p> <p>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 cloxacillin (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.</p>

Clinical Review
 Michelle M. Chuen, M.D.
 NDA #22-192
 Iloperidone

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	<p><u>SEPTICAEMIA</u></p> <p>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 septicæmia 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.</p> <p>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.</p>

Clinical Review
 Michelle M. Chuen, M.D.
 NDA #22-192
 Iloperidone

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	<u>DIABETES MELLITUS</u> 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	<u>SUDDEN DEATH DUE TO CARDIO-RESPIRATORY FAILURE</u> 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	<u>PYLORUS OCCULSION</u> 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.

Clinical Review
 Michelle M. Chuen, M.D.
 NDA #22-192
 Iloperidone

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	<u>ACUTE RENAL FAILURE</u> 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	<u>SUICIDE</u> 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	<u>STRUCK BY AUTOMOBILE</u> 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.

Clinical Review
 Michelle M. Chuen, M.D.
 NDA #22-192
 Iloperidone

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 ^c	200	1	Yes	<u>SUDDEN CARDIAC ARREST</u> 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	<u>VOLVULUS</u> 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.

Clinical Review
 Michelle M. Chuen, M.D.
 NDA #22-192
 Iloperidone

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	<u>PNEUMONIA</u> 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 (Septicemia¹²)

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 ($3.0-3.7 \times 10^9$ cells/L; reference range $4.1-12.3 \times 10^9$ cells/L).
3. On Study Day 310, the patient had a normal WBC count (8.2×10^9 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 (5.9×10^9 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.

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 patient's 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 [Orthostatic¹⁸ 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 (Orthostatic¹⁹ 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 symptoms²⁰)]

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 extrasystole 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 patient's 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 pressure²³)

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 patient's 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)

QTc Parameter	Iloperidone		Ziprasidone		Placebo	
	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 movements²⁴, 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. $\geq 5\%$ 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.

APPEARS THIS WAY ON ORIGINAL

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 (75.1%)	377 (80.2%)	378 (78.3%)	329 (84.1%)	1084 (80.7%)	112 (94.9%)	240 (78.4%)	130 (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 (5.3%)	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 variables²⁵ 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 (l/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.

Clinical Review
Michelle M. Chuen, M.D.
NDA #22-192
Iloperidone

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

	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 \geq 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 \geq 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 \leq 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 \geq 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 trials²⁸, 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.

	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)	
3005 509 1004	35/Black	10	397	394	tx dc	abortion	event occurred on Study Day 112; patient dc'd study drug on unspecified date without notifying the investigator ectopic pregnancy

Data Source: ISS Appendix 6

d-b=double blind; dc=discontinuation; tx=treatment

^aOne day posttreatment

^bLast 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
ILF3000									
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)
ILF3002									
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
ILF3003									
625 1021	25/F/Asian	12	259	256	2-3 12-18 mg	Gastritis, hypokalemia	Hospitalized Study drug dc'd		Suicide attempt
ILF3004									
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
ILF3005									
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)								
< 30 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%)
≥ 30 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%)
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	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)
Time period								
Mean (±SD), days	26.0 (13.71)	209.5 (294.73)	293.4 (317.14)	80.6 (123.39)	229.4 (296.29)	173.0 (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 (39.2%)	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. Approximately³¹ 420 CRF's were submitted, and the undersigned reviewer randomly selected 8 patients³² (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".

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, thiorazine, 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, extrapyramidal 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 maculopapular, 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 ≥ 120 bpm, pulse rate increase ≥ 15 bpm, SBP ≤ 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 3000³⁴
BASELINE DEMOGRAPHICS, RANDOMIZED POPULATION³⁵

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 score³⁶ (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.

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 regimens 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 to 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
<i>Age (yr) n</i>					
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
<i>Sex – n (%)</i>					
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)
<i>Race – n (%)</i>					
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.

<i>DSM-IV diagnosis</i>					
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)
<i>Baseline BPRS-total score</i>					
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 score⁴⁰ (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 Week	Ilo 4-8 mg			Ilo 10-16 mg			Ris			Pho		
	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.