

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

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

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

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

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

#### *Efficacy Results*

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

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<sup>43</sup> This information was not provided for ITT patients.

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

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

### *Conclusions*

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

### Study 3005

#### *Investigators/Sites*

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

#### *Objectives*

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

#### *Patient Sample*

Important inclusion criteria were:

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

- clinically relevant improvement compared with screening was detected, the placebo run-in period was extended until the patient's psychiatric status returned back to a level comparable with screening. If this improvement persisted for 7 additional days (i.e., total of 10 days of placebo run-in), the patient was not allowed to enter the study and a re-evaluation of the patient's psychiatric diagnosis was performed
- had a rating of at least "4" ("moderate") on at least 3 of the following 5 symptoms on the PANSS Positive Syndrome: delusions, conceptual disorganization, hallucinatory behavior, grandiosity and suspiciousness/persecution
  - was in need of psychiatric treatment
  - had vital signs measurements within normal ranges, defined for healthy adults as supine blood pressure in the range of 100-160 mm Hg systolic and 60-95 mm Hg diastolic, with a supine radial pulse of 60-100 beats per minute (bpm)
  - was to have no medical contraindication for oral treatment with iloperidone or risperidone, as confirmed by medical history, physical examination, electrocardiogram (ECG), and clinical laboratory tests, which were within the normal range, or, if abnormal, judged not to be clinically significant

The following were relevant exclusion criteria:

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

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

*Design*

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

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

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

Ilo=iloperidone; Ris=risperidone; Pbo=placebo

<sup>a</sup> Placebo run-in period lasted a minimum of 3 days; the last day of placebo run-in period was baseline (Day 0)

<sup>b</sup> Titration target dose

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

- \_ toleration of study medication
- \_ lack of worsening

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

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

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

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

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

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

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

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

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

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

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

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

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

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

#### *Efficacy Assessments*

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

#### *Efficacy Analysis*

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

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

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

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

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

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

#### *Baseline Demographics*

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

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<sup>44</sup> This information was not provided for the ITT population.

**TABLE 10.1.4 : STUDY 3005 BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS, RANDOMIZED POPULATION<sup>45</sup>**

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

Source: Dr. Phillip Dinh, Statistical Reviewer

*Baseline Severity of Illness*

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

<sup>45</sup> This information was not provided for the ITT population.

<sup>46</sup> This information was not provided for the ITT population.

### *Patient Disposition*

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

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

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

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

### *Dosing Information*

Dosing information is displayed in the following table.

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<sup>47</sup> Of note, all patients who received at least one dose of double-blind study medication also had at least one subsequent safety evaluation.

<sup>48</sup> This information was not provided for the safety population.

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

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

**Notes:**

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

*Concomitant Medications*

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

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

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

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

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

The following concomitant medications were permitted for the placebo run-in period and the short-term double-blind phase of the study for the treatment of insomnia:

- Chloral hydrate (prn, 500 mg p.o., up to 2000 mg/d total); or
- Zolpidem (prn, 5-10 mg/d p.o.). In countries where zolpidem was not available, another short half-life hypnotic was acceptable.

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

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

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

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

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

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

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

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

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<sup>49</sup> This information was not provided for ITT patients.

### *Efficacy Results*

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

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

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

### *Conclusions*

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

## Study 3101

### *Investigators/Sites*

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

### *Objectives*

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

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

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

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

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

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

#### *Patient Sample*

Important inclusion criteria were:

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

The following were relevant exclusion criteria:

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

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

#### *Design*

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

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

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

All patients were to be hospitalized during the 4 weeks of the short-term, double-blind study (Days 1 to 28). Day passes could be allowed at the Investigator's discretion during Weeks 3 and 4 to patients who had a responsible caregiver who could provide a stable residence. This information was to be documented in the source documents. On Weeks 3 and 4, three day passes were allowed for each week (maximum of 6 passes total). These passes could not be granted in consecutive days (e.g., a patient was not able to receive a weekend pass for Saturday and Sunday).

Patients who were granted day passes were required to be at the hospital for dosing. Caregivers were advised to follow all of the protocol requirements. Patients could have unlimited supervised outings with study staff personnel during Weeks 2 to 4. One emergency supervised outing could be granted by the Investigator during Week 1, if needed.

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

#### *Efficacy Assessments*

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

#### *Efficacy Analysis*

Per the original protocol, the ITT patients were those who:

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

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

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

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

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

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

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

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

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

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

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

*Baseline Demographics*

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

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

*Baseline Severity of Illness*

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

*Patient Disposition*

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

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

<sup>51</sup> This information was not provided for the ITT population.

<sup>52</sup> Figures may not add up to 100% due to rounding.

<sup>53</sup> This information was not provided for the ITT population.

<sup>54</sup> This information was not provided for the ITT population.

<sup>55</sup> Of note, all patients who received at least one dose of double-blind study medication also had at least one subsequent safety evaluation.

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

#### *Dosing Information*

This was a fixed dose study.

#### *Concomitant Medications*

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

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

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

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

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

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<sup>56</sup> This information was not provided for the safety population.

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

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

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

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

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

<sup>57</sup> This information was not provided for the MITT population.

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

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

#### *Efficacy Results*

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

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

#### *Conclusions*

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

#### Study B202

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

#### *Investigators/Sites*

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

#### *Objectives*

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

#### *Patient Sample*

Important inclusion criteria were:

- age 18 to 55 years

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

The following were relevant exclusion criteria:

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

### *Design*

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

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

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

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

The following concomitant medications were permitted throughout the study:

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

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

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

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

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

#### *Efficacy Assessments*

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

*Efficacy Analysis*

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

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

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

*Efficacy Results*

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

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

*Conclusions*

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

**10.2 Line-by-Line Labeling Review**

See section 9.4.

APPEARS THIS WAY ON ORIGINAL

### 10.3 Appendix to Individual Study Reports

#### APPENDIX 10.3.1: LIST OF INVESTIGATORS FOR STUDY 3000

Site	Last Name	First Name	Affiliation	Address	City	State	ZIP
502	Daniel	David	Clinical Studies-Washington	6066 Leesburg Pike, 6 <sup>th</sup> Floor	Falls Church	VA	22041
504	Ferguson	James	Pharmacology Research Clinic	448 East 6400 South, Suite 200	Salt Lake City	UT	84107
505	Hartford	James	Hartford Research Group	10550 Montgomery Road, Suite 20	Cincinnati	OH	45242
506	Iqbal	Naveed	Montefiore Medical Center	Department of Psychiatry, 111 East 210th Street, Klau Basement	Bronx	NY	10467
507	Lesem	Michael	Cleghorn-Lesem Research Clinic	6750 West Loop South, Suite 1050	Bellaire	TX	77401
508	Litman	Robert	The Center for Behavioral Health Research	14915 Brochart Road, Suite 250	Rockville	MD	20850
509	Merideth	Charles	Affiliated Research Institute	8880 Rio San Diego Drive, Suite 1090	San Diego	CA	92108
510	Potkin	Steven	UCI Medical Center	101 The City Drive South	Orange	CA	92866
511	Rosenthal	Murray	Behavioral and Medical Research	3625 Ruffin Road, Suite 100	San Diego	CA	92123
518	Brown	David	Community Clinical Research	4411 Medical Parkway	Austin	TX	78756
519	Buckley	Peter	Case Western Reserve University, Department of Psychiatry	University Hospitals of Cleveland, 11100 Euclid Ave.	Cleveland	OH	44106
521	Chou	James	New York University Medical Center/ Bellevue Hospital Center	Department of Psychiatry, 462 First Avenue, Room 20W13A	New York	NY	10016
523	Miller Ereshefsky	Alexander Larry	Clinical Research Unit, San Antonio State Hospital	6711 S. New Braunfels	San Antonio	TX	78223
525	Reid (replaced Grissom) Grissom	Timothy Christine	Clinical Studies, Melbourne	1360 Sarno Road, Suite B	Melbourne	FL	32935
526	Hafez	Hisham	Foundation Medical Partners at Southern New Hampshire Health Systems, Institute for Clinical Research at the Medical Center	Ten Prospect Street	Nashua	NH	03060
527	Hamner	Mark	Ralph H. Johnson VA Medical Center, Psychiatry Service (116)	109 Bee Street	Charleston	SC	29401

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

Site	Last Name	First Name	Affiliation	Address	City	State	ZIP
529	Kang	Jasbir	Western Pennsylvania Psychiatric Center	150 Pleasant Drive, Suite G-5	Center Twp.	PA	15001
530	Kanof (satellite site was not distinguished by patient numbering)	Philip	VA Medical Center, Psychiatry Services (4-116A)	3601 S. Sixth Avenue	Tucson	AZ	85723
531	Bartzokis McClain	George Catina	VA Medical Center	2200 Fort Roots Drive, Building 170 Room 2N101 (116A-NLR)	North Little Rock	AR	72114
532	Kingsbury	Steven	Dallas VA North Texas Health Care System (116A)	450D S. Lancaster Road	Dallas	TX	75216
533	Kolin	Irving	Orlando Regional Healthcare System	1065 West Morse Blvd., Suite 202	Winter Park	FL	32769
536	Riesenberg	Robert	Atlanta Center for Medical Research	625 Dekalb Industrial Way	Decatur	GA	30033
537	Reist	Christopher	VA Long Beach Healthcare System, Department of Mental Health 06/116A	5901 E. Seventh Street	Long Beach	CA	90822
538	Risch	Samuel	Medical University of South Carolina, Institute of Psychiatry, 502-North	67 President Street	Charleston	SC	29425
540	Shillcutt	Samuel	Department of Psychiatry and Behavioral Sciences, Mercer University School of Medicine	1508 College Street	Macon	GA	31207
541	Sokolski De Silva	Kenneth Himasiri	Affiliated Research Institute	801 N. Tustin Avenue, Suite 501	Santa Ana	CA	92705
543	Steinbook	Richard	University of Miami School of Medicine, Dept. of Psychiatry	1695 NW 9 <sup>th</sup> Avenue, Room 2101	Miami	FL	33136
544	Tapp	Andre	VA Puget Sound Health Care System, Mental Health Service (116)	American Lake Division, Bldg 7A, Rm 129	Tacoma	WA	98493
545	Tran-Johnson	Tram	California Neuropsychopharmacology Clinical Research Institute	10737 Camino Ruiz, Suite 200	San Diego	CA	92126
546	Udelman	Harold	Biomedical Stress Research	45 East Osborn Road	Phoenix	AZ	85012
547	Vieweg	Victor	Hunter Holmes McGuire VA Medical Center	Psychiatry Service (116A) 1201 Broad Rock Boulevard	Richmond	VA	23249
548	Wassef	Adel	Harris County Psychiatry Center	2800 S. MacGregor Way	Houston	TX	77021

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

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

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

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

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

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

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

Change is calculated as pre-post baseline value so that a positive change indicates improvement.

+ Based on t test using the ANCOVA model.

\* p < 0.05 (two-tailed).

\*\* Ilo (8mg+12mg)/2 is a treatment contrast to test the average of 8 mg group and 12 mg group versus placebo.

Adj. Change = Least squared mean change from the ANCOVA model.

Details of the analysis are found in the statistical appendix (Appendix 5.1).

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

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

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

Change is calculated as pre-post baseline value so that a positive change indicates improvement.

\* Based on t test using the ANCOVA model.

\*\* P < 0.05 (two-tailed).

\*\* Ilo (8mg+12mg)/2 is a treatment contrast to test the average of 8 mg group and 12 mg group versus placebo.

Adj. Change = least squared mean change from the ANCOVA model.

Details of the analysis are found in the statistical appendix (Appendix 5.1).

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

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

Change is calculated as pre-post baseline value so that a positive change indicates improvement.

+ Based on t test using the ANCOVA model.

\* p < 0.05 (two-tailed).

\*\* Ilo (8mg+12mg)/2 is a treatment contrast to test the average of 8 mg group and 12 mg group versus placebo.

Adj. Change = Least squared mean change from the ANCOVA model. Details of the analysis are found in the statistical appendix (Appendix 5.1).

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

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

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**APPENDIX 10.3.5: LIST OF INVESTIGATORS FOR STUDY 3004**

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

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

Site	Last name	First name	Affiliation	Address	City	State <sup>1</sup>	C <sup>2</sup>	ZIP
214	Rataemane,	Solomon	Oranje Hospital, Research Unit	Victoria Road	Makgerbe	Bloemfontein	ZA	9300
216	Ramjee,	Paresh	Vista Psychiatric Clinic	135 Gerhard Street	Centurion		ZA	0157
506	Lesem,	Michael	Claghorn-Lesem Research Clinic, Inc.	6750 West Loop South, Suite 1050	Bellaire	TX	USA	77401
510	Potkin,	Steve	UCI Medical Center	101 The City Drive South	Orange	CA	USA	92668
511	Rosenthal,	Murray	Behavioral & Medical Research, LLC	3625 Ruffin Road, Suite 100	San Diego	CA	USA	92123
536	Riesenberg,	Robert	Atlanta Center for Medical Research	625 Dekalb Industrial Way	Decatur	GA	USA	30033
545	Tran-Johnson,	Tram	California Neuropsychopharm acology, Clinical Research Institute	10737 Camino Ruiz, Suite 230	San Diego	CA	USA	92126
569	Jaffe,	Richard	Belmont Center for Comprehensive Treatment	4200 Monument Road	Philadelphia	PA	USA	19131
601	Ainslie,	George	VA Medical Center, Coatesville, Psychiatry 38-116A	1400 Black Horse Hill Road	Coatesville	PA	USA	19320- 2096
602	Bark,	Nigel	Schizophrenic Research Unit Ward 19, Bronx Psychiatric Center	1500 Waters Place	Bronx	NY	USA	10461
603	Berry,	Sally	Emory University School of Medicine, Department of Psychiatry	1707 Uppergate Drive, NE, Room 403	Atlanta	GA	USA	30322
604	Brenner,	Ronald	Neurobehavioral Research, Inc.	144 Grove Ave.	Cedarhurst	NY	USA	11516
605	Crayton,	John	Biologic Psychiatry Section 116A.7, Psychiatry Services 116A.7	Hines V.A. Hospital	Hines	IL	USA	60141
606	Dolgovff,	Robert	Berkeley Therapy Institute	1749 Martin Luther King Jr. Way	Berkeley	CA	USA	94709
607	Grumet,	Ross	Charter Behavioral Health System of Atlanta at Midtown, LLC	819 Juniper Street NE	Atlanta	GA	USA	30308
608	Halaxis,	Angelos	Dept of Psychiatry and Human Behavior, University Of Mississippi Medical Center	2500 North State Street	Jackson	MS	USA	39216- 4505
609	Huey,	Leighton	Department of Psychiatry, University of Connecticut Health Center	263 Farmington Ave.	Farmington	CT	USA	06030
611	Menza,	Matthew	UMDNJ Robert Wood Johnson Medical School, Department Of Psychiatry	675 Hoes Lane- D321	Piscataway	NJ	USA	08854
612	Mofsen,	Rick	Clinical Research Associates	3535 South Jefferson Avenue, Suite 304	St. Louis	MO	USA	63118

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

\* p-values are not adjusted for multiple comparisons

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## APPENDIX 10.3.10: LIST OF INVESTIGATORS FOR STUDY 3005

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NDA #22-192  
Iloperidone

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NDA #22-192  
Iloperidone

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NDA #22-192  
Iloperidone

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NDA #22-192  
Iloperidone

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NDA #22-192  
Iloperidone

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

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

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

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

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

Source: Post-text Table 9.1-2



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

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

Change is calculated as pre-post baseline value so that a positive change indicates improvement.

\* Based on t test using the ANCOVA model.

† p < 0.05 (two-tailed).

Adj. Change: least squares mean change from the ANCOVA model.

Change SD: least squares mean change from the ANCOVA model.

Details of the analysis are found in the statistical appendix (Appendix 5.1).

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

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

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

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

\* p-values are not adjusted for multiple comparisons

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

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

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

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

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NDA #22-192  
Iloperidone

**APPENDIX 10.3.17: LIST OF INVESTIGATORS FOR STUDY 3101**

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b(4)

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b(4)

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b(4)

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b(4)

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029	Larry Ereshefsky		California Clinical Trials Medical Group 1509 Wilson Terrace 55 Wing, Main Floor Glendale, CA 91206	22
030	Mark Lerman		Alexian Brothers Center for Psychiatric Research 1721 Moon Lake Blvd Suite 109 Hoffman Estate, IL 60194	5
031	Jason Baron		MedLabs Research of Houston, Inc 6260 Westpark Dr Suite 322 Houston, TX 77057	4
032	John Gilliam		International Clinical Research Associates, LLC 1601 Rolling Hills Dr Suite 201 Richmond, VA 23229-5011	11
033	David Flaherty		Segal Institute for Clinical Research, Atlantic Shores Hospital 1065 NE 125th St Suite 417 North Miami, FL 33161	15

b(4)

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

Site No.	Investigator Name	Sub-Investigator(s) Name	Site Address	Number of Enrolled Patients
034	Michael Schwartz	[REDACTED]	College Hospital Costa Mesa/USCRC 301 Victoria St Costa Mesa, CA 92627	12
037	Stephen Volk		California Clinical Trials Medical Group 15625 Lakewood Blvd Paramount, CA 90723	28
038	Edward Weissberg		Center for Behavioral Health, LLC Fellowship House 707 Saint Paul St Baltimore, MD 21202	20
101	Vinay L. Barhale		Shanti Nursing Home Kanchanwadi Paithan Road Aurangabad 431005 India	7
103	Lakshman Shankarlal Dutt		K.M. School of Post Graduate Medicine and Research NHL Municipal Medical College Sheth Vadilal Sarabhai General Hospital Ellis Bridge Ahmedabad, Gujarat 380006 India	6

b(4)

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

Site No.	Investigator Name	Sub-Investigator(s) Name	Site Address	Number of Enrolled Patients
104	Shiv Kumar Guatam Sharma		Department of Psychiatry S.M.S. Medical College Jaipur 302004 India	3
107	Sanjay Phadke		HCJMRI, Jehangir Hospital 32 Sassoon Rd Pune (Maharashtra) 411001 India	6
108	Nadukuru Raju		Government Hospital for Mental Care Chinawaltair, Visakha Patnam 530002 India	3
109	Ramanathan Sathianathan		Madras Medical College & Government General Hospital Department of Psychiatry Chennai 600003 India	6
110	Podila Satya Venkata Narasimha Sharma		Department of Psychiatry Kasturba Hospital Post Box No 7 Manipal 576104 Karnataka India	4

b(4)

Site No.	Investigator Name	Sub-Investigator(s) Name	Site Address	Number of Enrolled Patients
111	Padmasudhakar Thatikonda		SV Medical College Tirupati Andhra Pradesh 517507 India	5
112	Jitendra Kumar Trivedi		K.G. Medical University Department of Psychiatry KG Medical University Chowk Lucknow U.P. 226003 India	8

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

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

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

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

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

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

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

Source: Post-text Table 9.2.1-2a.

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

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

Visit	Ilo N = 283	Zip N = 144	Ebo N = 140	Pairwise Mean Differences		
				Ilo vs Ebo	Zip vs Ebo	Ilo vs Zip
Day 7 (Week 1)						
n	281	142	139			
ESL Mean	92.96	91.07	90.42			
ESL SD	13.13	11.47	11.25			
Mean Change	-4.20	-6.52	-3.98			
Change SD	9.45	23.21	9.82			
Adj. Change	-4.27	-6.65	-4.11	-0.16	-2.54	2.38
Adj. Change (SE)	0.62	0.87	0.89	1.09	1.24	1.38
95% C.I.	-5.49, -8.06	-8.37, -4.94	-5.55, -2.86	-2.80, 1.98	-4.98, -0.10	5.26, 4.49
p-value ++				0.892	0.341	0.028
Day 10						
n	254	131	125			
ESL Mean	92.75	90.44	89.98			
ESL SD	13.40	11.46	10.97			
Mean Change	-7.86	-5.55	-6.42			
Change SD	11.33	24.68	11.06			
Adj. Change	-7.52	-5.68	-6.15	-1.78	-6.74	1.56
Adj. Change (SE)	0.73	1.02	1.06	1.80	1.46	1.26
95% C.I.	-9.86, -6.69	-11.65, -7.88	-9.28, -4.06	-4.33, 0.77	-6.62, -0.87	-0.52, 4.54
p-value +				0.166	0.009	0.109
Interaction Adj ESL-by-Treatment = 0.056 0						
Adj ESL 25th Percentile	-6.38	-6.36	-5.42	0.550	0.605	0.988
Adj ESL 50th Percentile	-7.68	-5.33	-6.02	0.254	0.328	3.195
Adj ESL 75th Percentile	-9.15	-12.68	-6.72	0.127	3.001	0.018

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

Day 14 (Week 2)		228		123		118	
n		52.21	90.40	88.98			
ESL Mean		12.82	11.44	10.96			
ESL SD		-9.79	-11.18	-7.31			
Mean Change		12.66	16.10	14.81			
Change SD		-9.59	-11.62	-7.21			
Adj. Change		0.87	1.21	1.27			
Adj. Change (SE)		-11.71, -5.28	-14.01, -9.24	-9.70, -4.72			
95% C.I.							
p-value +							
Interaction Adj ESL-by-Treatment = 0.095 @							
Adj ESL 25th Percentile		-7.62	-7.10	-5.62			
Adj ESL 50th Percentile		-9.71	-11.09	-7.02			
Adj ESL 75th Percentile		-11.80	-15.97	-8.42			
p-value ++							
Day 21 (Week 3)		220		106		135	
n		92.20	91.00	89.34			
ESL Mean		12.61	11.80	10.34			
ESL SD		-12.07	-14.31	-9.67			
Mean Change		13.67	16.22	15.46			
Change SD		-12.25	-14.81	-10.26			
Adj. Change		0.94	1.88	1.38			
Adj. Change (SE)		-14.10, -10.40	-17.46, -12.16	-12.86, -7.43			
95% C.I.							
p-value ++							

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

Day 28 (Week 4)	n	200	102	93
BSL Mean		51.90	90.53	89.67
BSL SD		12.52	11.96	10.62
Mean Change		-14.92	-15.52	-12.04
Change SD		13.96	17.03	15.68
Adj. Change		-14.89	-16.44	-12.84
Adj. Change (SE)		0.58	1.63	1.49
95% C.I.		-16.88, -12.64	-19.16, -13.85	-15.78, -9.90
p-value ++				-5.82, 1.81
				0.334
				-7.60, 3.41
				2.04
				-3.60
				1.84
				1.72
				-1.56, 5.23
				0.286

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

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

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

‡ p-value < 0.05; † p-value < 0.01 (2 tailed)

Notes:

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

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

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

PANSS-T = Positive and Negative Syndrome Scale total score; MMRM = Mixed Model Repeated Measures; ITT = intent-to-treat.

<sup>a</sup> P < 0.05 (2-tailed) compared with placebo based on MMRM analysis with baseline as covariate.

<sup>b</sup> P < 0.01 (2-tailed) compared with placebo based on MMRM analysis with baseline as covariate.

Source: Post-text Table 9.2.1-2b.

**APPENDIX 10.3.21: LIST OF INVESTIGATORS FOR STUDY B202**

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

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

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

Visit	Placebo			Iloperidone (2 mg BID)			Iloperidone (4 mg BID)				
	N	Mean Chg <sup>1</sup>	P-Value <sup>2</sup>	N	Mean Chg <sup>1</sup>	P-Value <sup>2</sup>	P-value <sup>3</sup>	N	Mean Chg <sup>1</sup>	P-Value <sup>2</sup>	P-value <sup>3</sup>
Baseline	31			32				28			
Day 8	5	4.00	0.659	6	8.50	0.258	0.748	4	-21.3	0.185	0.083
Day 15	29	-6.97	0.034	29	-3.03	0.413	0.380	25	-10.3	0.001	0.388
Day 22	23	-9.65	0.012	26	-7.19	0.015	0.311	21	-12.5	0.002	0.906
Day 29	21	-8.62	0.069	24	-12.9	<0.001	0.873	16	-17.5	0.002	0.246
Day 36	18	-14.3	0.022	22	-14.2	<0.001	0.570	16	-22.5	0.001	0.337
Day 43	17	-18.4	0.010	22	-12.1	0.003	0.243	15	-26.8	<0.001	0.429
EP <sup>4</sup>	31	-6.68	0.146	32	-4.13	0.275	0.621	28	-18.2	<0.001	0.077

<sup>1</sup> Mean Chg. = means change from baseline

<sup>2</sup> P-value = Within treatment Groups

<sup>3</sup> P-Value = Between Treatment Groups (placebo and 2 mg BID or 4 mg BID)

<sup>4</sup> EP = Last Observation Carried Forward

Baseline Mean Scores: Placebo = 97.71, Iloperidone (2 mg) BID = 90.56, Iloperidone (4 mg bid) = 100.5

APPEARS THIS WAY ON ORIGINAL

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

##### APPENDIX 10.4.1: CLINICAL INVESTIGATORS WITH UNOBTAINABLE FINANCIAL DISCLOSURE INFORMATION

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

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

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

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

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

## 10.5 Appendix to Integrated Review of Safety (Section 7)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Notes:

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

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

SOC <sup>a</sup> 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)
<i>N (%) of pts who dc'd due to TEAE</i>	32 (5.3%)	25 (5.3%)	24 (5.0%)	19 (4.9%)	68 (5.1%)	9 (7.6%)	19 (6.2%)	16 (10.7%)
Gastrointestinal	1 (0.2%)	1 (0.2%)	5 (1.0%)	2 (0.5%)	80.6%	0	4 (1.3%)	1 (0.7%)
Nausea	0	1 (0.2%)	2 (0.4%)	0	3 (0.2%)	0	1 (0.3%)	0
Nervous system	6 (1.0%)	5 (1.1%)	6 (1.2%)	4 (1.0%)	15 (1.1%)	3 (2.5%)	10 (3.3%)	6 (4.0%)
Dizziness	2 (0.3%)	0	3 (0.6%)	1 (0.3%)	4 (0.3%)	0	3 (1.0%)	0
Syncope	0	1 (0.2%)	1 (0.2%)	1 (0.3%)	3 (0.2%)	0	1 (0.3%)	0
Psychiatric	15 (2.6%)	11 (2.3%)	6 (1.2%)	3 (0.8%)	20 (1.5%)	4 (3.4%)	3 (1.0%)	7 (4.7%)
Psychotic disorder	6 (1.0%)	3 (0.6%)	2 (0.4%)	1 (0.3%)	6 (0.4%)	2 (1.7%)	1 (0.3%)	3 (2.0%)
Schizophrenia	2 (0.3%)	1 (0.2%)	2 (0.4%)	0	3 (0.2%)	0	1 (0.3%)	0
Reproductive system & breast	1 (0.2%)	1 (0.2%)	4 (0.8%)	3 (0.8%)	8 (0.6%)	0	3 (1.0%)	0
Erectile dysfunction	0	1 (0.2%)	1 (0.2%)	1 (0.3%)	3 (0.2%)	0	1 (0.3%)	0
Respiratory, thoracic & mediastinal	0	3 (0.6%)	1 (0.2%)	1 (0.3%)	5 (0.4%)	0	0	1 (0.7%)
Dyspnoea	0	1 (0.2%)	1 (0.2%)	1 (0.3%)	3 (0.2%)	0	0	0
Vascular disorders	0	1 (0.2%)	4 (0.8%)	2 (0.5%)	7 (0.5%)	0	0	0
Orthostatic hypotension	0	1 (0.2%)	3 (0.6%)	1 (0.3%)	5 (0.4%)	0	0	0

Data Source: ISS Table 9.1.2

Table includes data from double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.

Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; TEAE=treatment-emergent adverse event; ZIP=ziprasidone.

Patients who experienced multiple AEs within the same SOC were counted only once for that same SOC.

Patients who experienced the same AE multiple times within the same SOC were counted only once for the corresponding Preferred Term based on the highest degree of relationship.

Adverse events sorted alphabetically by SOC; within each SOC, the preferred term is presented by decreasing order of frequency in the combined ILO group.

Percentages are based on the total number of patients within each treatment/dose group.

<sup>a</sup> Complete SOC names have been abbreviated because of space constraints.

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

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

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

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

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

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

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

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

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

Lymphocytes (%)								
n [a]	534 (91.0%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	38 (7.1%)	25 (6.2%)	20 (4.4%)	20 (5.4%)	65 (5.3%)	5 (4.5%)	8 (2.9%)	11 (7.7%)
Low [b]	33 (6.2%)	21 (5.2%)	31 (6.8%)	28 (7.3%)	80 (6.5%)	11 (9.8%)	29 (10.3%)	8 (5.6%)
High/Low [b]	0	0	0	0	0	0	0	0
Monocytes (10e9/L)								
n [a]	532 (90.6%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	10 (1.9%)	13 (3.2%)	9 (2.0%)	4 (1.1%)	26 (2.1%)	6 (5.4%)	9 (3.3%)	0
Low [b]	25 (4.7%)	4 (1.0%)	6 (1.3%)	27 (7.3%)	37 (3.0%)	1 (0.9%)	1 (0.4%)	19 (13.4%)
High/Low [b]	0	0	0	0	0	0	0	0
Monocytes (%)								
n [a]	534 (91.0%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	14 (2.6%)	24 (6.0%)	16 (3.5%)	5 (1.3%)	45 (3.7%)	9 (8.0%)	9 (3.3%)	0
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
Neutrophils, Total (10e9/L)								
n [a]	398 (67.8%)	401 (85.3%)	435 (90.1%)	114 (29.2%)	950 (70.7%)	112 (94.9%)	276 (90.2%)	0
High [b]	82 (20.6%)	46 (11.5%)	68 (15.6%)	24 (21.1%)	138 (14.5%)	21 (18.8%)	74 (26.8%)	0
Low [b]	20 (5.0%)	28 (7.0%)	25 (5.7%)	6 (5.3%)	59 (6.2%)	5 (4.5%)	5 (1.8%)	0
High/Low [b]	1 (0.3%)	0	0	0	0	1 (0.9%)	0	0
Neutrophils, Total (%)								
n [a]	398 (67.8%)	401 (85.3%)	435 (90.1%)	114 (29.2%)	950 (70.7%)	112 (94.9%)	276 (90.2%)	0
High [b]	51 (12.8%)	35 (8.7%)	60 (13.8%)	15 (13.2%)	110 (11.6%)	18 (16.1%)	50 (18.1%)	0
Low [b]	19 (4.8%)	20 (5.0%)	21 (4.8%)	2 (1.8%)	43 (4.5%)	5 (4.5%)	5 (1.8%)	0
High/Low [b]	0	0	0	0	0	0	0	0
Platelet Count, (10e9/L)								
n [a]	528 (89.9%)	398 (84.7%)	451 (93.4%)	372 (95.1%)	1221 (90.8%)	110 (93.2%)	272 (88.9%)	140 (93.3%)
High [b]	36 (6.8%)	15 (3.8%)	20 (4.4%)	22 (5.9%)	57 (4.7%)	4 (3.6%)	13 (4.8%)	7 (5.0%)
Low [b]	5 (0.9%)	5 (1.3%)	11 (2.4%)	5 (1.3%)	21 (1.7%)	2 (1.8%)	8 (2.9%)	2 (1.4%)
High/Low [b]	0	1 (0.3%)	0	0	1 (0.1%)	0	0	0
Red Blood Cells, (10e12/L)								
n [a]	533 (90.8%)	403 (85.7%)	454 (94.0%)	372 (95.1%)	1229 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	8 (1.5%)	2 (0.5%)	1 (0.2%)	8 (2.2%)	11 (0.9%)	2 (1.8%)	1 (0.4%)	3 (2.1%)
Low [b]	46 (8.6%)	76 (18.9%)	94 (20.7%)	63 (16.9%)	233 (19.0%)	18 (16.1%)	35 (12.7%)	10 (7.0%)
High/Low [b]	0	0	0	0	0	0	0	0
White Blood Cells, (10e9/L)								
n [a]	533 (90.8%)	402 (85.5%)	454 (94.0%)	372 (95.1%)	1228 (91.4%)	112 (94.9%)	276 (90.2%)	142 (94.7%)
High [b]	89 (16.7%)	43 (10.7%)	54 (11.9%)	38 (10.2%)	135 (11.0%)	18 (16.1%)	63 (22.8%)	16 (11.3%)
Low [b]	23 (4.3%)	18 (4.5%)	20 (4.4%)	9 (2.4%)	47 (3.8%)	0	7 (2.5%)	4 (2.8%)
High/Low [b]	0	0	0	0	0	0	0	0
Glycohemoglobin A1C, (% TL HB)								
n [a]	128 (21.8%)	2 (0.4%)	19 (3.9%)	244 (62.4%)	265 (19.7%)	0	0	136 (90.7%)
High [b]	11 (8.6%)	0	1 (5.3%)	28 (11.5%)	29 (10.9%)	0	0	19 (14.0%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0

Data Source: ISS Table 24.1.2

Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.

HAL=haloperidol; ILO=iloperidone; n=number of patients with measurable value for each analyte; PBO=placebo; RIS=risperidone; ZIP=ziprasidone.

High and Low categories are based on worst value observed during the treatment period.

Categories High, Low, and High/Low are considered mutually exclusive.

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

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

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

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

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

<b>High Density Lipoprotein (mmol/L)</b>								
n [a]	138 (23.5%)	2 (0.4%)	19 (3.9%)	259 (66.2%)	280 (20.8%)	0	0	142 (94.7%)
High [b]	138 (100.0%)	2 (100.0%)	19 (100.0%)	259 (100.0%)	280 (100.0%)	0	0	142 (100.0%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
<b>LDH (U/L)</b>								
n [a]	538 (91.7%)	401 (85.3%)	453 (93.8%)	375 (95.9%)	1229 (91.4%)	111 (94.1%)	272 (88.9%)	141 (94.0%)
High [b]	29 (5.4%)	24 (6.0%)	31 (6.8%)	4 (1.1%)	59 (4.8%)	10 (9.0%)	18 (6.6%)	2 (1.4%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
<b>Low Density Lipoprotein (Calc) (mmol/L)</b>								
n [a]	135 (23.0%)	2 (0.4%)	18 (3.7%)	248 (63.4%)	268 (19.9%)	0	0	133 (90.0%)
High [b]	45 (33.3%)	1 (50.0%)	5 (27.8%)	97 (39.1%)	103 (38.4%)	0	0	37 (27.4%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
<b>Prolactin (ug/L)</b>								
n [a]	333 (56.7%)	289 (61.5%)	206 (42.7%)	247 (63.2%)	742 (55.2%)	93 (78.8%)	92 (30.1%)	137 (91.3%)
High [b]	39 (11.7%)	81 (28.0%)	76 (36.9%)	63 (25.5%)	220 (29.6%)	80 (86.0%)	86 (93.5%)	22 (16.1%)
Low [b]	1 (0.3%)	3 (1.0%)	0	0	3 (0.4%)	0	0	2 (1.5%)
High/Low [b]	0	0	0	0	0	0	0	0
<b>Triglycerides (mmol/L)</b>								
n [a]	541 (92.2%)	407 (86.6%)	457 (94.6%)	376 (96.2%)	1240 (92.3%)	112 (94.9%)	278 (90.8%)	142 (94.7%)
High [b]	131 (24.2%)	104 (25.6%)	128 (28.0%)	116 (30.9%)	348 (28.1%)	32 (28.6%)	70 (25.2%)	38 (26.8%)
Low [b]	0	0	0	0	0	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
<b>Thyroid Stimulating Hormone (TSH) (mU/L)</b>								
n [a]	14 (2.4%)	16 (3.4%)	8 (1.7%)	19 (4.9%)	43 (3.2%)	2 (1.7%)	5 (1.6%)	10 (6.7%)
High [b]	0	1 (6.3%)	0	0	1 (2.3%)	0	0	0
Low [b]	0	1 (6.3%)	0	0	1 (2.3%)	0	0	0
High/Low [b]	0	0	0	0	0	0	0	0
<b>Uric Acid (umol/L)</b>								
n [a]	541 (92.2%)	407 (86.6%)	458 (94.8%)	376 (96.2%)	1241 (92.3%)	112 (94.9%)	278 (90.8%)	142 (94.7%)
High [b]	83 (15.3%)	97 (23.8%)	115 (25.1%)	25 (6.6%)	237 (19.1%)	24 (21.4%)	42 (15.1%)	2 (1.4%)
Low [b]	21 (3.9%)	6 (1.5%)	6 (1.3%)	17 (4.5%)	29 (2.3%)	2 (1.8%)	2 (0.7%)	10 (7.0%)
High/Low [b]	0	0	0	0	0	0	0	0
<b>Electrolytes</b>								
<b>Calcium, (mmol/L)</b>								
n [a]	541 (92.2%)	407 (86.6%)	457 (94.6%)	376 (96.2%)	1240 (92.3%)	112 (94.9%)	278 (90.8%)	141 (94.0%)
High [b]	36 (6.7%)	9 (2.2%)	20 (4.4%)	26 (6.9%)	55 (4.4%)	3 (2.7%)	14 (5.0%)	11 (7.8%)
Low [b]	7 (1.3%)	28 (6.9%)	13 (2.8%)	3 (0.8%)	44 (3.5%)	5 (4.5%)	9 (3.2%)	1 (0.7%)
High/Low [b]	0	0	0	0	0	0	0	0
<b>Chloride, (mmol/L)</b>								
n [a]	541 (92.2%)	407 (86.6%)	457 (94.6%)	376 (96.2%)	1240 (92.3%)	112 (94.9%)	278 (90.8%)	142 (94.7%)
High [b]	13 (2.4%)	2 (0.5%)	4 (0.9%)	30 (8.0%)	36 (2.9%)	0	3 (1.1%)	15 (10.6%)
Low [b]	6 (1.1%)	5 (1.2%)	5 (1.1%)	2 (0.5%)	12 (1.0%)	1 (0.9%)	4 (1.4%)	0
High/Low [b]	0	0	0	0	0	0	0	0
<b>CO<sub>2</sub> (Bicarbonate), (mmol/L)</b>								
n [a]	539 (91.8%)	407 (86.6%)	458 (94.8%)	375 (95.9%)	1240 (92.3%)	112 (94.9%)	277 (90.5%)	141 (94.0%)
High [b]	26 (4.8%)	32 (7.9%)	27 (5.9%)	2 (0.5%)	61 (4.9%)	12 (10.7%)	18 (6.5%)	0
Low [b]	14 (2.6%)	2 (0.5%)	4 (0.9%)	13 (3.5%)	19 (1.5%)	1 (0.9%)	3 (1.1%)	5 (3.5%)
High/Low [b]	0	0	0	0	0	0	0	0
<b>Inorganic Phosphorus, (mmol/L)</b>								
n [a]	538 (91.7%)	401 (85.3%)	454 (94.0%)	375 (95.9%)	1230 (91.5%)	111 (94.1%)	272 (88.9%)	142 (94.7%)
High [b]	35 (6.5%)	17 (4.2%)	14 (3.1%)	53 (14.1%)	84 (6.8%)	1 (0.9%)	11 (4.0%)	34 (23.9%)
Low [b]	5 (0.9%)	6 (1.5%)	8 (1.8%)	3 (0.8%)	17 (1.4%)	0	5 (1.8%)	2 (1.4%)
High/Low [b]	0	0	0	0	0	0	0	0
<b>Magnesium, (mmol/L)</b>								
n [a]	403 (68.7%)	405 (86.2%)	438 (90.7%)	117 (29.9%)	960 (71.4%)	112 (94.9%)	278 (90.8%)	0
High [b]	0	1 (0.2%)	1 (0.2%)	0	2 (0.2%)	0	0	0
Low [b]	0	1 (0.2%)	0	1 (0.9%)	2 (0.2%)	1 (0.9%)	0	0
High/Low [b]	0	0	0	0	0	0	0	0

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

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

Data Source: ISS Table 25.1.2

Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.

HAL=haloperidol; ILO=iloperidone; n=number of patients with measurable value for each analyte; RIS=risperidone; ZIP=ziprasidone.

High and Low categories are based on worst value observed during the treatment period.

Values are presented as n (%). Percentages are calculated based on the number of patients with a normal baseline measurement and at least one postbaseline measurement. Only patients who had paired data are included.

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

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

Data Source: ISS Table 26.1.2

Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.

BL=baseline; HAL=haloperidol; ILO=iloperidone; n=number of patients with measurable value for each analyte; PBO=placebo; RIS=risperidone; ZIP=ziprasidone. Percentages are based on the total number of observed patients within each treatment group.

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

Vital Sign	Lower Limit	Upper Limit
Pulse Rate (bpm)	$\leq 50$ bpm	$\geq 120$ bpm
	$\geq 15$ bpm decrease	$\geq 15$ bpm increase
	$\leq 50$ bpm and a decrease of $\geq 15$ bpm	$\geq 120$ bpm and an increase of $\geq 15$ bpm
Systolic Blood Pressure (mm Hg)	$\leq 90$ mm Hg	$\geq 150$ mm Hg
	$\geq 10$ mm Hg decrease	$\geq 10$ mm Hg increase
	$\leq 90$ mm Hg and a decrease of $\geq 10$ mm Hg	$\geq 150$ mm Hg and an increase of $\geq 10$ mm Hg
Diastolic Blood Pressure (mm Hg)	$\geq 10$ mm Hg decrease	$\geq 10$ mm Hg increase
	$\leq 65$ mm Hg	$\geq 100$ mm Hg
	$\leq 65$ mm Hg and a decrease of $\geq 10$ mm Hg	$\geq 100$ mm Hg and an increase of $\geq 10$ mm Hg
Temperature ( $^{\circ}$ C)	$\leq 33.1^{\circ}$ C	$\geq 38.3^{\circ}$ C
		$\geq 38.3^{\circ}$ C and a change of $\geq 1.1^{\circ}$ C
Body weight change from baseline	Decrease of $\geq 7\%$	Increase of $\geq 7\%$

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

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

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

Pulse Rate Assessment	Placebo	ILO 4-8 mg/d	ILO 10-16 mg/d	ILO 20-24 mg/d	ILO Comb.	HAL 5-20 mg/d	RIS 4-8 mg/d	ZIP 160 mg/d
Number of patients <sup>a</sup>	581 (99.0%)	460 (97.9%)	480 (99.4%)	391 (100.0%)	1331 (99.0%)	118 (100.0%)	301 (98.4%)	149 (99.3%)
≥120 bpm	49 (8.4%)	156 (33.9%)	120 (25.0%)	142 (36.3%)	418 (31.4%)	23 (19.5%)	72 (23.9%)	17 (11.4%)
>15 bpm increase	303 (52.2%)	344 (74.8%)	307 (64.0%)	377 (70.8%)	928 (69.7%)	75 (63.6%)	197 (65.4%)	90 (60.4%)
≤50 bpm	12 (2.1%)	5 (1.1%)	11 (2.3%)	4 (1.0%)	20 (1.5%)	0	8 (2.7%)	6 (4.0%)
≥15 bpm decrease	249 (42.9%)	181 (39.3%)	189 (39.4%)	133 (34.0%)	503 (37.8%)	60 (50.8%)	126 (41.9%)	64 (43.0%)
≥120 bpm and an increase of ≥15 bpm <sup>b</sup>	39 (6.7%)	146 (31.7%)	111 (23.1%)	132 (33.8%)	389 (29.2%)	21 (17.8%)	66 (21.9%)	15 (10.1%)
≤50 bpm and a decrease of ≥15 bpm <sup>b</sup>	5 (0.9%)	2 (0.4%)	8 (1.7%)	2 (0.5%)	12 (0.9%)	0	5 (1.7%)	3 (2.0%)

<sup>a</sup> Number of patients with at least one postbaseline vital signs assessment.

<sup>b</sup> Percentages are based on the total number of observed patients within each treatment group.

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

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

Source: ISS Table 15.5.2, ISS Table 27.1.2

Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.

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

<sup>a</sup> Percentages are based on the total number of patients within each treatment group.

<sup>b</sup> Percentages are based on the total number of observed patients within each treatment group.

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

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

Temperature as measured during any point during period of observation. C=Celsius; F=Fahrenheit.

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

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

Weight (kg)	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 5-20 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
Distribution of Percent Weight Change								
0-<7%	279 (48.4%)	277 (60.9%)	310 (64.4%)	252 (64.5%)	839 (63.2%)	63 (53.4%)	183 (60.6%)	100 (67.1%)
7-<10%	19 (3.3%)	28 (6.2%)	29 (6.0%)	44 (11.3%)	101 (7.6%)	5 (4.2%)	22 (7.3%)	6 (4.0%)
10-<15%	6 (1.0%)	17 (3.7%)	23 (4.8%)	22 (5.6%)	62 (4.7%)	1 (0.8%)	12 (4.0%)	2 (1.3%)
15-<20%	0	3 (0.7%)	4 (0.8%)	3 (0.8%)	10 (0.8%)	0	2 (0.7%)	0
>=20%	0	1 (0.2%)	2 (0.4%)	3 (0.8%)	6 (0.5%)	0	0	0
>=7% increase	25 (4.3%)	49 (10.8%)	58 (12.1%)	72 (18.4%)	179 (13.3%)	6 (5.1%)	36 (11.9%)	8 (5.4%)
>=7% decrease	14 (2.4%)	10 (2.2%)	4 (0.8%)	1 (0.3%)	15 (1.1%)	3 (2.5%)	4 (1.3%)	2 (1.3%)
% Change at Endpoint (SD)	-0.0 (3.68)	1.8 (4.74)	2.5 (4.59)	3.3 (4.45)	2.5 (4.63)	0.2 (4.92)	1.8 (4.46)	1.4 (3.37)

Data Source: ISS Table 16.1.2, ISS Table 16.2.2, ISS Table 28.1.2

Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.

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

Vital Signs	Placebo (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)
Study Group 2	581 (99.0%)	460 (97.9%)	480 (99.4%)	391 (100.0%)	1331 (99.0%)	118 (100.0%)	301 (98.4%)	149 (99.3%)
Patients with at Least 1 Postbaseline Assessment*	581 (99.0%)	460 (97.9%)	480 (99.4%)	391 (100.0%)	1331 (99.0%)	118 (100.0%)	301 (98.4%)	149 (99.3%)

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

Patients with Orthostatic Response <sup>b</sup>	334 (57.5%)	375 (81.5%)	343 (71.5%)	266 (68.0%)	984 (73.9%)	87 (73.7%)	194 (64.5%)	80 (33.7%)
Patients with Sustained Orthostasis <sup>b</sup>	107 (18.4%)	187 (40.7%)	167 (34.8%)	151 (38.6%)	505 (37.9%)	39 (33.1%)	81 (26.9%)	17 (11.4%)

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

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

<sup>a</sup> Percentages are based on the total number of patients within each treatment group.

<sup>b</sup> Percentages are based on the total number of observed patients within each treatment group.

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

- QTcF interval  $\geq$  450 msec
- QTcF interval  $\geq$  480 msec
- QTcF interval  $\geq$  500 msec
- Heart rate > 100 bpm
- Heart rate < 50 bpm
- PR interval > 200 msec
- QRS interval > 100 msec

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

QTcF Parameter	Placebo (N=587)	ILO 4-8 mg/d (N=470)	ILO 10-16 mg/d (N=483)	ILO 20-24 mg/d (N=391)	ILO Comb. (N=1344)	HAL 15 mg/d (N=118)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
<b>Fridericia's formula</b>								
Mean ( $\pm$ SD) baseline value, msec	384.6 (22.12)	381.3 (21.92)	382.9 (23.71)	386.2 (21.37)	383.4 (22.5)	390.2 (20.24)	378.8 (22.75)	388 (18)
Mean ( $\pm$ SD) maximum value, msec	393.2 (22.22)	394.8 (21.54)	396.1 (22.89)	408.5 (22.76)	399.5 (23.2)	402.5 (19.92)	390.1 (21.59)	410.3 (21.83)
<b>N (%) with QTc:</b>								
$\geq$ 450 msec, all patients	6 (1.1%)	18 (1.7%)	34 (2.3%)	17 (3.9%)	69 (2.3%)	6 (1.1%)	1 (0.4%)	8 (4.4%)
$\geq$ 450 msec, females	5 (2.9%)	15 (3.8%)	18 (3.5%)	11 (11.2%)	44 (4.3%)	4 (2.1%)	1 (1.1%)	7 (15.2%)
$\geq$ 450 msec, males	1 (0.3%)	3 (0.4%)	16 (1.7%)	6 (1.8%)	25 (1.3%)	2 (0.6%)	0	1 (0.7%)
$\geq$ 480 msec, all patients	0	0	3 (0.7%)	0	3 (0.2%)	0	0	0
$\geq$ 480 msec, females	0	0	1 (0.6%)	0	1 (0.3%)	0	0	0
$\geq$ 480 msec, males	0	2 (0.3%)	12 (1.3%)	6 (1.8%)	20 (1.0%)	2 (0.6%)	0	2 (1.5%)
$\geq$ 500 msec, all patients	0	0	0	0	0	0	0	0
$\geq$ 500 msec, females	0	0	0	0	0	0	0	0
$\geq$ 500 msec, males	0	0	4 (0.4%)	0	4 (0.2%)	0	0	0
N (%) with $\geq$ 15% increase from BL in QTc at any TP	17 (3.1%)	118 (10.9%)	217 (14.7%)	57 (13.1%)	392 (13.1%)	43 (8.1%)	16 (5.8%)	15 (8.2%)
N (%) with $\geq$ 30 msec change in QTc at any TP	107 (19.7%)	441 (40.6%)	757 (51.4%)	239 (55.1%)	1437 (48.0%)	198 (37.3%)	82 (29.7%)	91 (50.0%)
N (%) with $\geq$ 60 msec change in QTc at any TP	15 (2.8%)	96 (8.8%)	184 (12.5%)	53 (12.2%)	333 (11.1%)	38 (7.2%)	14 (5.1%)	14 (7.7%)

Data Source: ISS Table 17.6.2. Note that ISS Table 17.6.2 omits a parameter if there were no occurrences for that particular parameter in any treatment group.

Table includes data from all phases of Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101 and period 1 of Study 2328  
BL=baseline; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; TP=time point; ZIP=ziprasidone

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

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

Data Source: ISS Table 30.1.2.

Table includes data from all patients enrolled in double-blind phase of placebo-controlled studies 3000, 3004, 3005 and 3101.

BL=baseline; Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; TP=time point; ZIP=ziprasidone.

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/s/

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

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

**Review and Evaluation of Clinical Data  
NDA #22-192**

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

**I. Background**

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

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

**II. Clinical Data**

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

*HIGHLIGHTS OF PRESCRIBING INFORMATION*

The bullets should be modified to state

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

*HIGHLIGHTS OF PRESCRIBING INFORMATION/Indications and Usage*

This section should be modified to state

┌

b(4)

└  
b(5)

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

20 Page(s) Withheld

       Trade Secret / Confidential (b4)

X Draft Labeling (b4)

X Draft Labeling (b5)

       Deliberative Process (b5)

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/s/

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

Ni Aye Khin  
7/8/2008 07:34:15 PM  
MEDICAL OFFICER

I disagree with some of Dr. Chuen's labeling recommendations;  
see memo to file for additional comments.

**Review and Evaluation of Clinical Data  
NDA #22-192**

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

**I. Background**

Iloperidone is a mixed 5-HT<sub>2A/D2</sub> antagonist developed for the treatment of schizophrenia. Data from 9 controlled studies, including that for the 597 patients in the short-term, double-blind phase of Study VP-VYV-683-3101 (also known as Study 3101), were integrated to form the safety database for this NDA. This safety update focuses on data for the 173 patients who were treated with iloperidone in the long-term, open-label phase of Study 3101. Of note, the clinical safety cut-off date for the original NDA was December 4, 2006, while the clinical cut-off date for this safety update was May 4, 2007, after the database for Study 3101 had been locked (on March 21, 2007).

**II. Data Source and Exposure**

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

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

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

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

- <sup>a</sup> Treatment groups (iloperidone, ziprasidone, and placebo) are those assigned in the short-term, double-blind phase. For example, ziprasidone/iloperidone represents a patient being assigned to ziprasidone during the short-term, double-blind phase and iloperidone during the long-term, open-label phase. In the long-term, open-label phase, all patients received iloperidone (12 mg/day or 24 mg/day).
- <sup>b</sup> Percentages are based on the total number of patients who completed the short-term, double-blind phase in each treatment group.
- <sup>c</sup> Percentages are based on the total number of patients who entered the long-term, open-label phase in each treatment group.
- <sup>d</sup> The investigator determined the primary reason for withdrawal. Only one reason was recorded on the CRF.
- <sup>e</sup> Percentages are based on the total number of patients who withdrew during long-term, open-label phase within each treatment group.

Of note, the mean modal dose of iloperidone during the long-term, open-label phase was 21.6 mg/day, and the mean duration of treatment was 103 days.

In this safety update, the exposure data from the long-term, open-label phase of Study 3101 was added to the integrated safety database from the NDA. Of the 173 patients who entered the long-term, open-label extension phase, 87 were newly exposed to iloperidone (i.e. they switched from double-blind placebo or ziprasidone). This increased the number of patients who received iloperidone in the integrated clinical studies from 3210 to 3297. The sponsor provided the following table, titled: "Duration of Treatment, Updated Safety Data—Study Group 1 (Safety Population).

Duration of Treatment Time period	Placebo (N = 587)	ILO 4-8 mg/d (N = 1227)	ILO 10-16 mg/d (N = 1562)	ILO 20-24 mg/d (N = 508)	ILO Total (N = 3297)	HAL 5-20 mg/d (N = 546)	RIS 4-8 mg/d (N = 311)	ZIP 160 mg/d (N = 184)
Mean (±SD), days	26.0 (13.71)	209.5 (294.73)	293.4 (317.14)	80.6 (123.39)	229.4 (296.29)	175.0 (155.92)	66.1 (87.84)	20.0 (9.16)
<b>Cumulative duration of treatment:</b>								
>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.

Of note, at the effective dose of 20-24 mg/day, only 64 patients were exposed for >6 months and only 22 patients were exposed for >12 months.

Also, with the addition of these 87 patients, exposure to the 20-24 mg/day dose increased from 452 to 508 patients, for an additional 39.55 patient years. The sponsor provided the following table, titled: “Cumulative Patient-Years of Exposure to Study Drug, Updated Safety Data—Study Group 1 (Safety Population).

Treatment Group	Number Treated	Cumulative Extent of Exposure (Patient-Years)
Placebo	587	41.71
Iloperidone <sup>a</sup>	3297	2070.31
4-8 mg/day	1227	703.66
10-16 mg/day	1562	1254.58
20-24 mg/day	508	112.07
Haloperidol	546	261.57
Risperidone	311	56.30
Ziprasidone	184	10.09

Data Source: ISS Table 33.1.1

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

<sup>a</sup> The total dose a patient received was calculated as a function of the modal dose. The modal dose for the patient was based on the daily dose that the patient received most frequently during the phase of study. If there was no true modal dose (e.g., infrequent doses such as during titration), the highest dose received was conservatively chosen as the modal dose.

### III. Adverse Events

#### Deaths

One death occurred during the long-term, open-label phase of Study 3101. Patient VP-VYV-683-112-0009, a 30-year-old man of Asian Indian decent, died suddenly on Study Day 65. He had received ziprasidone during the short-term, double-blind study phase and had been receiving open-label iloperidone for a total of 37 days when he died. Two days before his death, his dose of iloperidone was reduced from 24 mg/day to 12 mg/day due to mild restless and mild akathisia. The patient’s family reported that on the day of his death, he went for a walk. About one-half hour after his return, he lost consciousness, and his breathing was labored. The family rushed the patient to a nearby hospital, where he was pronounced dead on arrival. The cause of death remains unclear—no autopsy was performed, and the patient was cremated. Of note, the patient was not a smoker and “did not have a history of anaphylaxis, allergy, asthma, physical disorder, or any drug abuse/dependence. There was no family history of sudden death or myocardial infarction.” Therefore, this reviewer cannot rule out that this death was related to the study drug.

Of note, the sponsor did conduct a mortality analysis based on patient years of exposure for the integrated Phase 2/3 iloperidone clinical studies in the ISS database (not including the data from 120-Day Safety Update), including deaths during treatment or within 30 days of treatment discontinuation. Based on published results, the mortality per 100 patient years was lower in the combined iloperidone group compared with ziprasidone, quetiapine, and aripiprazole. In addition, the sponsor also conducted an analysis of the rate of sudden, unexpected deaths in the original iloperidone NDA safety database and

compared it to the sudden death rates for other antipsychotic drugs, as presented in the NDA clinical review for ziprasidone. In their analysis, iloperidone had a comparable rate of sudden, unexpected deaths to risperidone and a lower rate than that for sertindole, ziprasidone, olanzapine, and quetiapine.

#### Other Serious Adverse Events

Fourteen patients had a treatment-emergent serious adverse event. Most of these were related to exacerbation of underlying psychiatric disorders. The sponsor included the following table, titled: "Patient List of Nonfatal Serious Adverse Events—Study 3101 OLE."

Treatment at Onset	Patient Number	Age/Sex/Race	Preferred Term	Start day/End day	Drug Relation	Severity
<b>Iloperidone/Iloperidone</b>						
ILO 12 mg/day	005-0013	40/M/BL	Schizophrenia	119/127	Unrelated	Severe
	005-0027	41/M/BL	Major depression	107/118	Unrelated	Severe
ILO 24 mg/day	008-0002	49/F/WH	Schizophrenia	36/43	Unrelated	Severe
	008-0010	55/M/WH	Psychotic disorder	64/69	Unrelated	Severe
	019-0016	44/M/BL	Psychotic disorder	65/74	Unrelated	Severe
	019-0017	45/M/BL	Psychotic disorder	201/217	Unrelated	Severe
	019-0021	27/M/BL	Psychotic disorder	115/129	Unrelated	Severe
	019-0033	34/M/WH	Schizophrenia	82/90	Unrelated	Mild
	031-0005	38/M/BL	Schizophrenia	57/65	Unrelated	Moderate
<b>Ziprasidone/Iloperidone</b>						
Titration	012-0005	25/M/BL	Excoriation	34/—	Unrelated	Moderate
			Periorbital hematoma	34/—	Unrelated	Moderate
			Drug abuser	34/35	Unrelated	Moderate
ILO 24 mg/day	008-0007	48/M/BL	Psychotic disorder	97/104	Unrelated	Severe
	014-0029	28/M/WH	Suicidal ideation	76/84	Unrelated	Severe
<b>Placebo/Iloperidone</b>						
ILO 12 mg/day	005-0030	32/M/BL	Psychotic disorder	91/95	Unrelated	Moderate
ILO 24 mg/day	101-0001	21/M/AS	Dengue fever	103/122	Unrelated	Severe

Data Source: 3101 OLE CSR Post-text Filtered Listing 10.2.2-1.

All events are treatment emergent.

AM = American Indian or Alaska Native; AS = Asian; BL = Black American; F = female; ILO = iloperidone; M = male; NA = Native Hawaiian or other Pacific Island; OLE = open-label extension; OT = Other; WH = White

Of note, patient number 012-0005 received the excoriation and periorbital hematoma from a fall, but the reason for the fall is not given. The same day, he also used cocaine.

#### Adverse Events Leading to Permanent Discontinuation of Study Drug

Overall, adverse events led to permanent discontinuation of study drug in 12.1% of patients in the open-label treatment phase of Study 3101. The most frequent of such events were in the system-organ class of Psychiatric Disorders (11/173; 6.4%). The only events that led to treatment discontinuation in 1% or more of iloperidone-treated patients were drug abuse (2/173; 1.2%), headache (2/173, 1.2%), psychotic disorder (4/173, 2.3%), and schizophrenia (3/173, 1.7%). The sponsor included the following table, titled: "Adverse Events That Led to Withdrawal, by Double-Blind Treatment Group—Study 3101 OLE."

Body System/ Preferred Term <sup>a</sup>	ILO-ILO (N = 86) <sup>b</sup>	ZIP-ILO (N = 46) <sup>b</sup>	PBO-ILO (N = 41) <sup>b</sup>	ILO Total (N = 173)
N (%) withdrawn for AE	12 (14.0%)	8 (17.4%)	4 (9.8%)	24 (13.9%)
<b>General disorders and administration site conditions</b>	0	1 (2.2%)	0	1 (0.6%)
Sudden death	0	1 (2.2%)	0	1 (0.6%)
<b>Injections and infestations</b>	0	0	1 (2.4%)	1 (0.6%)
Dengue fever	0	0	1 (2.4%)	1 (0.6%)
<b>Investigations</b>	1 (1.2%)	0	0	1 (0.6%)
Glycosylated haemoglobin increased	1 (1.2%)	0	0	1 (0.6%)
<b>Metabolism and nutrition disorders</b>	1 (1.2%)	0	0	1 (0.6%)
Hyponatraemia	1 (1.2%)	0	0	1 (0.6%)
<b>Musculoskeletal and connective tissue disorders</b>	1 (1.2%)	0	0	1 (0.6%)
Muscle tightness	1 (1.2%)	0	0	1 (0.6%)
<b>Nervous system disorders</b>	1 (1.2%)	2 (4.3%)	1 (2.4%)	4 (2.3%)
Headache	1 (1.2%)	1 (2.2%)	0	2 (1.2%)
Dizziness	0	1 (2.2%)	0	1 (0.6%)
Somnolence	0	0	1 (2.4%)	1 (0.6%)
<b>Psychiatric disorders</b>	7 (8.1%)	3 (6.5%)	1 (2.4%)	11 (6.4%)
Psychotic disorder	2 (2.3%)	1 (2.2%)	1 (2.4%)	4 (2.3%)
Schizophrenia	2 (2.3%)	1 (2.2%)	0	3 (1.7%)
Hallucination, auditory	1 (1.2%)	0	0	1 (0.6%)
Major depression	1 (1.2%)	0	0	1 (0.6%)
Schizophrenia, paranoid type	1 (1.2%)	0	0	1 (0.6%)
Suicidal ideation	0	1 (2.2%)	0	1 (0.6%)
<b>Renal and urinary disorders</b>	1 (1.2%)	0	1 (2.4%)	2 (1.2%)
Renal impairment	0	0	1 (2.4%)	1 (0.6%)
Urinary incontinence	1 (1.2%)	0	0	1 (0.6%)
<b>Respiratory, thoracic and mediastinal disorders</b>	0	1 (2.2%)	0	1 (0.6%)
Throat tightness	0	1 (2.2%)	0	1 (0.6%)
<b>Social circumstances</b>	1 (1.2%)	1 (2.2%)	0	2 (1.2%)
Drug abuse	1 (1.2%)	1 (2.2%)	0	2 (1.2%)

Data Source: 3101 OLE CSR Post-text Table 10.1.4-1b

OLE = open-label extension; SOC = system-organ class

<sup>a</sup> SOCs are sorted alphabetically; within each SOC, the preferred term is presented by decreasing order of total frequency.

<sup>b</sup> Percentages are based on the total number of patients within the treatment group.

Patients experiencing the same AE multiple times are only counted once for the corresponding preferred term. Similarly, patients experiencing multiple AEs within the same SOC are counted only once for that SOC.

### Treatment-emergent Adverse Events

As this study was an open-label extension, without a placebo control group, this reviewer went over the complete “Treatment Emergent Adverse Events” table to look for any clinically significant, unexpected (for this class of medications) findings. The only such finding was “hemoglobin decreased” in 16/173 (9.2% of the subjects). However, the sponsor did not provide, in any organized fashion, further information on who these subjects were and the degree of their decreased hemoglobin. Of note, this reviewer

informally discussed this finding with the primary reviewer. She is aware of this particular issue and plans to address it in her NDA review.

#### **IV. Literature Search**

As a sufficiently comprehensive literature search was lacking in the original NDA, the sponsor included one as part of the 120-Day Safety Update. This search was conducted on November 13, 2007 using the PubMed search engine to identify any recent publications on iloperidone. The sponsor concludes that in this search, “no previously unreported adverse events were found. None of the publications in the literature search revealed any new safety concerns, or affected the known safety profile, of iloperidone.” This reviewer briefly surveyed all the articles in the literature search (e.g. looking at abstracts and under adverse events, if present). Most of the articles involved the drug’s pharmacology or pharmacokinetics. No new adverse events of any concern could be found in these articles.

#### **V. Conclusions and Recommendations**

Based on a review of the 120-Day Safety Update, there were no new safety findings that would preclude approval of this application. However, as the primary review team is aware, even with the additional 87 patients treated with iloperidone in the open-label extension of Study 3101, there is insufficient exposure at relevant doses (20-24 mg/day) in the safety database. Of note, during the open-label phase of Study 3101, an otherwise physically healthy 30-year-old man died suddenly for unclear reasons (no autopsy was performed). This reviewer cannot rule out that his death was related to study drug, such as from a drug-induced cardiac arrhythmia. Finally, under treatment-related adverse events, 9.2% of subjects had “hemoglobin decreased,” but the sponsor does not provide any further analysis of these subjects. The primary reviewer, Dr. Michelle Chuen, is already aware of and plans to address this issue in her review.

Phillip D. Kronstein, M.D.  
June 13, 2008

cc: HFD-130/ Kronstein  
Khin  
Laughren  
Updegraff  
Dubitsky

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Phillip D Kronstein  
6/13/2008 01:19:16 PM  
MEDICAL OFFICER

Ni Aye Khin  
6/25/2008 03:36:59 PM  
MEDICAL OFFICER  
See memo to file for additional comments.

**Interdisciplinary Review Team for QT Studies**  
**Response to Request for Consultation: QT Study Review**

<b>IND or NDA</b>	22-192
<b>Generic Name</b>	Iloperidone
<b>Sponsor</b>	Vanda Pharmaceuticals Inc.
<b>Indication</b>	Treatment of Schizophrenia
<b>Dosage Form</b>	Tablets
<b>Drug Class</b>	Psychotropic
<b>Therapeutic Dose</b>	Initial Treatment: 12 mg/day administered b.i.d. Maintenance Treatment: _____
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Not defined
<b>Application Submission Date</b>	27 November 2007
<b>Review Classification</b>	Standard NDA
<b>Date Consult Received</b>	29 November 2007
<b>Clinical Division</b>	DPP/HFD 130
<b>PDUFA Date</b>	27 July 2008

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**1 SUMMARY**

**1.1 OVERALL SUMMARY OF FINDINGS**

In this QT study the sponsor attempted to compare the effects of administering three doses (8 mg b.i.d., 12 mg b.i.d., and 24 mg QD) of iloperidone with ziprasidone (80 mg b.i.d.) and quetiapine (375 mg b.i.d.) on the QT interval. The effects of metabolic inhibition on iloperidone and the active comparators were also evaluated.

Iloperidone prolongs the QT interval. At all doses studied, the maximum mean increase in baseline-corrected QTcF was greater than 10 ms, the threshold for regulatory concern. In the presence of metabolic inhibition, there was further lengthening of the QTcF interval. However, the design of the study had significant limitations and as a result the QT-IRT finds that a *precise estimate of the effect* of administering iloperidone on the QT interval cannot be established.

The major limitations are as follows:

- This study was not a placebo-controlled study. There were two active controls, ziprasidone 80 mg b.i.d. and quetiapine 375 mg b.i.d., but the magnitude of their effects on the QT interval is not well characterized.
- All treatments were administered open-label. Thus, the study is subject to potential bias.

- Assay sensitivity could not be established. The study included two active comparators: quetiapine (375 mg b.i.d.) and ziprasidone (80 mg b.i.d.). Based on the FDA analysis of the exposure-response analysis for quetiapine in two other QT studies (Study A750-1001 in NDA 22,192 and Study R076477-SCH-1014 in NDA 21,999), it is expected that quetiapine will increase the QT interval in a concentration-dependent manner, with an approximate effect size of 7-10 ms for a mean C<sub>max</sub> of 1,000 to 1,200 ng/ml quetiapine. In this study, quetiapine did not prolong the QT interval despite achieving mean steady-state peak concentration of 826 ng/ml. Therefore, our confidence in the estimated effect size of administering iloperidone on QTc is low.

The QT-IRT does not have experience with ziprasidone and cannot establish assay sensitivity based on its effects on QTc.

- ECGs were not available for review.

## 1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- While none of the safety events identified to be of particular importance per ICH E-14 guidelines occurred in this study, one patient on ILO 12 mg b.i.d. did experience pre-syncope and sinus bradycardia.
- ECG acquisition and interpretation in this study had several limitations.
  - ECGs were not recorded in triplicate
  - ECG waveforms were not sent to the ECG warehouse for review.
- We do not recommend using metabolic inhibition with ketoconazole or paroxetine to assess the effects of supratherapeutic iloperidone concentrations on the QT interval because 1) ketoconazole itself prolongs the QT interval; 2) the metabolic profile of iloperidone will change with CYP3A4 and CYP2D6 inhibition; and 3) iloperidone may change the metabolism of ketoconazole or paroxetine. Furthermore, since this study did not include a placebo control, the observed increases in ΔQTc in treatment periods 2 and 3 are confounded by the co-administration of paroxetine and ketoconazole.

## 2 PROPOSED LABEL

The sponsor proposed the following label:

### 5.0 WARNINGS AND PRECAUTIONS

#### 5.2 QT Prolongation

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2   Page(s) Withheld

       Trade Secret / Confidential (b4)

  X   Draft Labeling (b4)

  X   Draft Labeling (b5)

       Deliberative Process (b5)

### 3 BACKGROUND

Iloperidone is a new chemical entity proposed for the treatment of schizophrenia. Iloperidone belongs to the chemical class of piperidinyl-benzisoxazole derivatives and has high (nM) affinity for 5HT<sub>2A</sub>/NE $\alpha$ 1/NE $\alpha$ 2c/D<sub>2</sub>/D<sub>3</sub>/5HT<sub>1A</sub> receptors in humans and acts as an antagonist at selected dopaminergic, serotonergic, and adrenergic receptors. The sponsor believes that it has effective antipsychotic activity with reduced liability for extrapyramidal symptoms, akathisia, prolactin elevation, sedation and weight gain.

#### 3.1 MARKET APPROVAL STATUS

Iloperidone is not approved for marketing in any country.

#### 3.2 PRECLINICAL INFORMATION

Source: Non-clinical Summary

The in vitro effects of iloperidone and its metabolites P95 and P88 in comparison with risperidone and ziprasidone were examined on mammalian cells stably transfected with cloned cDNA of the cardiac ion channel hERG using whole cell patch-clamp recordings. Blockade of hERG currents in vitro is an indication of the potential for QTc prolongation clinically (Study 008167). All test articles produced rapid, reversible blockade of hERG currents. The block potency rank order was iloperidone > ziprasidone~ P88 > risperidone > P95. Assessment of the blockade at near-physiological temperature showed an increase of the IC<sub>50</sub> value for the blockade for all test items except for risperidone. These data suggest that P95 is unlikely to contribute to the QT prolongation potential of iloperidone.

In dog Purkinje fibers paced at stimulation frequencies of 0.5 and 1 Hz, iloperidone and its metabolite P88 at a concentration of 0.1  $\mu$ M and above prolonged action potential duration. At the highest concentration tested (10  $\mu$ M), there appeared to be a depression of the plateau phase of the action potential. This may be attributed to a possible interaction with cardiac calcium channels at this concentration. There was also a reduction in maximum rate of depolarization at 3 Hz at this concentration, indicating a frequency-dependent interaction with cardiac sodium channels. When Purkinje fibers were exposed to P95 at concentration of 0.01, 0.1, 1 and 10  $\mu$ M, prolonged action potential duration at 10  $\mu$ M did not reach to the level of statistical significance; there was no prolongation seen at the concentration below or at 1  $\mu$ M.

These data indicate that iloperidone and its metabolite P88 at free plasma concentrations of 0.1  $\mu$ M and above are likely to have direct effects on the QRS complex, QT duration, and cardiac conduction. The metabolite P95 is less likely to have direct effects on the QRS complex or QT duration unless plasma concentrations in excess of 10  $\mu$ M are reached.

Iloperidone was also found to have potential hypotensive and vasodilatory effects similar to those of clozapine in normotensive and hypertensive rats and in conscious and anesthetized dogs. These effects appear to be due at least in part to  $\alpha$ 1-adrenergic receptor blockade. Apart from a transient increase in heart rate observed in some studies, no other notable hemodynamic effects (eg, cardiac output changes or ECG findings) were noted in rats or dogs. Metabolites P88, P89, and P95 were also found to exert hemodynamic effects similar to iloperidone, including decreasing blood pressure.

#### 3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Integrated Summary of Clinical Safety

The safety profile of iloperidone is based primarily on the integrated safety data from 4439 adult patients with schizophrenia (3210 exposed to iloperidone) enrolled in the double-blind phase of four Phase 3, randomized, placebo-controlled studies. Integrated safety data from 1944 adult patients enrolled in 5 additional active-controlled studies or who participated in the open-label extension phase of the placebo-controlled studies have also been included.

Study Group 1 included all patients enrolled in any phase of all 9 controlled studies combined. Study Group 2 included patients enrolled only in the double-blind phase of one of the 4 placebo-controlled studies combined. Study Group 3 included patients enrolled in the double-blind phase of one of the 8 active- or placebo-controlled studies combined. Study Group 4 included patients who received iloperidone in the open-label extension phase of one of 7 of the double-blind, controlled studies.

In total, 23 patients (15 iloperidone, one placebo, 3 active-control [2 risperidone, 1 haloperidol] and 4 not randomized; including treatment-related and unrelated to treatment) died while participating in the Iloperidone Clinical Program. Most of the deaths (n=13) occurred during the long-term, double-blind, or open-label treatment phase (Table 59). Five deaths were suicides. An additional 3 patients treated with iloperidone died of a cardiac event (sudden Cardiac arrest, sudden death due to Cardio-respiratory failure or Cardiac failure). All 3 cardiac events leading to death were determined by the investigators to be unrelated to study drug. All other causes of deaths occurred in 1 patient each.

In Study Group 1, *cardiac adverse events* (composite term) occurred in 9.2% of patients in the combined iloperidone group, which was higher than in the comparator groups (range, 3.5% to 4.2%), but similar to that in the ziprasidone group (11.4%). Among the three iloperidone dose groups, cardiac adverse events were reported more frequently in patients receiving ILO 20-24 mg/day (19.2%) than either of the 2 lower doses (7.5% each). This pattern was observed in both Study Groups 2 and 3. In Study Group 4, patients who previously received risperidone had the highest incidence of cardiac adverse events (8.5%), and those who received placebo, the lowest (4.3%).

In Study Group 1, *orthostatic hypotension or hypotension* was reported as an adverse event in 3.0% and 1.7% of patients, respectively, in the combined iloperidone group.

In Study Group 1, *seizures* were uncommon. Thirteen patients (0.4%) in the combined iloperidone group had a seizure some time during treatment, similar to the comparator groups (0.2% to 0.3%), except for ziprasidone (ISS Table 21.1.1). No seizures were reported in that group. Seizure was considered by the investigator to be drug related in 8 iloperidone-treated patients.

Across the entire ISS database a subset analysis was performed on only those patients who had an increase from baseline in QTc interval (using Study Group 1). The results showed that the mean maximum QTc interval durations remained within normal limits and were comparable across treatment groups (ranging from 392.86 ms to 408.90 ms). Similarly, mean increases and mean percent changes from baseline to worst QTcF value were also comparable (ranging from approximately 18 ms to approximately 29 ms and 5.0% to 8.0% across treatment groups, respectively). Moreover, there was no clinically relevant dose-related increase in mean QTc duration or in mean percent change from baseline among the 3 iloperidone dose groups. This pattern was observed for both Study Groups 2 and Study Group 3. In Study Group 4, the mean QTc durations were similar across groups, irrespective of prior double-blind treatment and remained within normal limits (ranging from 398.73 ms to 405.46 ms). However, the mean change from baseline to worst QTcF value was highest for patients who previously received haloperidol (36.9 ms, 10.2%) and lowest for patients who previously received placebo (22.0 ms, 5.9%) during double-blind treatment. Although QTcF interval

prolongation did appear to be more likely to occur with longer exposure to active treatment, it also appeared that the maximum effect during open-label iloperidone treatment plateaued at  $\leq 470$  ms.

Across the entire ISS database, 2 patients each had 1 episode in which their QTcF interval exceeded 500 ms. Both patients were men receiving open-label ILO 10-16 mg/day. However, both episodes were associated with confounding factors. One patient had a QTcF interval of 507 ms after overdosing on iloperidone (438 mg over 4 days), with no cardiac sequelae. After being treated in the hospital for extrapyramidal symptoms, the patient was discharged and resumed iloperidone treatment for an additional 11 months. The second patient has a QTcF interval of 508 ms while being treated in the intensive care unit for septic shock.

### **3.4 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of iloperidone's clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The sponsor submitted A TQT study report and associated electronic data sets. ECGs were not submitted to the ECG warehouse.

### **4.2 TQT STUDY**

#### **4.2.1 Protocol Number and Title**

Protocol ILO522 2328: A randomized, open-label, multicenter, 5-arm, safety evaluating the effect of oral iloperidone at doses of 8 mg b.i.d., 12 mg b.i.d., and 24 mg q.d. on QTc interval duration in the presence and absence of metabolic inhibition, relative to other antipsychotics (ziprasidone 80 mg b.i.d. and quetiapine 375 mg b.i.d., in the presence and absence of metabolic inhibition), in otherwise healthy patients diagnosed with schizophrenia or schizoaffective disorder.

#### **4.2.2 Study Dates**

November 27, 2001 to May 03, 2002

#### **4.2.3 Objectives**

The primary objective of the study is to characterize the effect of iloperidone at doses of 8 mg b.i.d. and 12 mg b.i.d. on the duration of the QTc interval in otherwise healthy patients diagnosed with schizophrenia or schizoaffective disorder.

The secondary objectives of this study were:

- to evaluate the effect of iloperidone on QTc interval duration when given as a 24 mg once-daily dose
- to evaluate the effect of iloperidone on QTc interval duration in the presence of inhibitors of iloperidone metabolism
- to evaluate the concentration-effect relationship of iloperidone and its primary metabolite (P88), on QTc interval duration

- to compare the effects of iloperidone on the QTc interval to the effects of the antipsychotics ziprasidone, quetiapine, and risperidone (following protocol Amendment 2, dated 09-Jan-2002, risperidone was removed from this comparison).

#### 4.2.4 Study Description

##### 4.2.4.1 Design

This was a multicenter, randomized, open-label, 5-arm study that included 5 periods: screening, taper, washout/baseline, treatment period 1 (dose escalation and steady state without metabolic inhibition), and treatment period 2 (addition of 1 metabolic inhibitor). Patients who received iloperidone underwent one additional period, treatment period 3, in which a second metabolic inhibitor was added.

**Table 1. Study Design (Treatment phase)**

Phase	Treatment phase		
Period	Treatment Period 1	Treatment Period 2	Treatment Period 3
Iloperidone 8 mg b.i.d.	Days 1-15	Days 16 – 23 (+paroxetine)	Days 24 – 28 (+paroxetine and ketoconazole)
Iloperidone 12 mg b.i.d.	Days 1-17	Days 18 –25 (+paroxetine)	Days 26 –30 (+paroxetine and ketoconazole)
Iloperidone 24 mg q.d.	Days 1-18	Days 19 –26 (+paroxetine)	Days 27 –31 (+paroxetine and ketoconazole)
Risperidone 4 mg b.i.d.	Days 1-13	Days 14 – 21 (+paroxetine)	-
Ziprasidone 80 mg b.i.d.	Days 1-10	Days 11 – 15 (+ketoconazole)	-
Quetiapine 375 mg b.i.d.	Days 1-12	Days 13 – 17 (+ketoconazole)	-

Note: following Amendment 2 (see Section 4.1), the risperidone treatment arm was removed from the trial.

(Source: Ilo522-2328-legacy report: Table 3-2, page 25)

##### 4.2.4.2 Controls

The study did not include a placebo control. Antipsychotics ziprasidone and quetiapine were used as active controls. However, no formal hypotheses were specified with regard to the active controls.

##### 4.2.4.3 Blinding

This study was an open-label study. However, a centralized blinded ECG reader was used in order to avoid any potential bias in interpretation of ECG results.

#### 4.2.5 Treatment Regimen

##### 4.2.5.1 Treatment Arms

The study included 5 treatment arms:

- Iloperidone Low (8 mg b.i.d.)

- Iloperidone High (12 mg b.i.d.)
- Iloperidone QD (24 mg q.d.)
- Quetiapine 375 mg b.i.d.
- Iloperidone 80 mg b.i.d.

Reviewer's Comment: Risperidone 4 mg b.i.d. was included originally, but removed under protocol amendment 2.

Dosing schedules for iloperidone and reference therapies are shown in Table 2 and Table 3.

**Table 2: Dosing Schedule for Iloperidone**

Day	Iloperidone LOW (8 mg b.i.d.)				Iloperidone HIGH (12 mg b.i.d.)				Iloperidone QD (24 mg q.d.)			
	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs
1	2	1	1		2	1	1		2	1	1	
2	2	1	1	1 ECG	2	1	1	1 ECG	2	1	1	1 ECG
3	4	2	2		4	2	2		4	2	2	
4	4	2	2		4	2	2		4	2	2	
5	8	4	4		8	4	4		8	4	4	
6	8	4	4		8	4	4		8	4	4	
7	12	6	6		12	6	6		12	6	6	
8	18 TD	8	8		16	8	8		12	12	-	
9	18	8	8		20	10	10		16	16	-	
10	18	8	8		24 TD	12	12		20	20	-	
11	18	8	8		24	12	12		24 TD	24	-	
12	18	8	8		24	12	12		24	24	-	
13	16	8	8	ECGs	24	12	12		24	24	-	
14	16	8	8	ECGs	24	12	12		24	24	-	
15	16	8	8	ECGs	24	12	12	ECGs	24	24	-	
16	16+P	8	8		24	12	12	ECGs	24	24	-	ECGs
17	16+P	8	8	1 ECG	24	12	12	ECGs	24	24	-	ECGs
18	16+P	8	8		24+P	12	12		24	24	-	ECGs
19	16+P	8	8		24+P	12	12	1 ECG	24+P	24	-	
20	16+P	8	8		24+P	12	12		24+P	24	-	1 ECG
21	16+P	8	8	ECGs	24+P	12	12		24+P	24	-	
22	16+P	8	8	ECGs	24+P	12	12		24+P	24	-	
23	16+P	8	8	ECGs	24+P	12	12	ECGs	24+P	24	-	
24	16+P +K	8	8		24+P	12	12	ECGs	24+P	24	-	ECGs
25	16+P +K	8	8	1 ECG	24+P	12	12	ECGs	24+P	24	-	ECGs
26	16+P +K	8	8	ECGs	24+P +K	12	12		24+P	24	-	ECGs
27	16+P +K	8	8	ECGs	24+P +K	12	12	1 ECG	24+P +K	24	-	
28	16+P +K	8	8	ECGs	24+P +K	12	12	ECGs	24+P +K	24	-	1 ECG
29	-	-	-		24+P +K	12	12	ECGs	24+P +K	24	-	ECGs
30	-	-	-		24+P +K	12	12	ECGs	24+P +K	24	-	ECGs
31	-	-	-						24+P +K	24	-	ECGs

TD = Target dose; P=paroxetine 20 mg q.d.; K=ketoconazole 200 mg b.i.d.

Note: Based on Amendment 2, the PM dose of ketoconazole was not given on the last day of study drug administration (see Section 4.1).

BOLD = Days of steady-state ECG evaluations

(Source: Ilo522-2328-legacy report: Table 3-2, page 25)

**Table 3: Dosing Schedule for Reference Therapies**

Day	Risperidone				Ziprasidone				Quetiapine			
	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs	Daily Dose (mg)	A.M. (mg)	P.M. (mg)	ECGs
1	2	1	1		40	20	20		50	25	25	
2	4	2	2	1 ECG	40	20	20	1 ECG	100	50	50	1 ECG
3	4	2	2		80	40	40		200	100	100	
4	8	3	3		80	40	40		300	150	150	
5	8	3	3		120	60	60		400	200	200	
6	8 TD	4	4		160 TD	80	80		500	250	250	
7	8	4	4		160	80	80		600	300	300	
8	8	4	4		160	80	80	ECGs	750 TD	375	375	
9	8	4	4		160	80	80	ECGs	750	375	375	
10	8	4	4		160	80	80	ECGs	750	375	375	ECGs
11	8	4	4	ECGs	160+ K	80	80		750	375	375	ECGs
12	8	4	4	ECGs	160+ K	80	80	1 ECG	750	375	375	ECGs
13	8	4	4	ECGs	160+ K	80	80	ECGs	750+ K	375	375	
14	8+P	4	4		160+ K	80	80	ECGs	750+ K	375	375	1 ECG
15	8+P	4	4	1 ECG	160+ K	80	80	ECGs	750+ K	375	375	ECGs
16	8+P	4	4		-	-	-		750+ K	375	375	ECGs
17	8+P	4	4		-	-	-		750+ K	375	375	ECGs
18	8+P	4	4		-	-	-		-	-	-	
19	8+P	4	4	ECGs	-	-	-		-	-	-	
20	8+P	4	4	ECGs	-	-	-		-	-	-	
21	8+P	4	4	ECGs	-	-	-		-	-	-	
22	-	-	-		-	-	-		-	-	-	
23	-	-	-		-	-	-		-	-	-	

TD = Target dose; P=paroxetine 20 mg q.d.; K=ketoconazole 200 mg b.i.d.

BOLD = Days of steady-state ECG evaluations

Note: Following Amendment 2, the risperidone treatment arm was removed, and the PM dose of ketoconazole was not given on the last day of study drug administration (see Section 4.1).

(Source: Ilo522-2328-legacy report: Table 3-6, page 35)

#### 4.2.5.2 Sponsor's Justification for Doses

The current study, CIL0522A2328, included doses of 8 mg b.i.d. and 12 mg b.i.d. in order to evaluate the effect of iloperidone on QTc at these higher doses. This study also evaluated the safety of 24 mg/d given q.d., as it was unknown whether higher peak concentrations and/or greater fluctuations in plasma concentrations would affect the QTc interval duration.

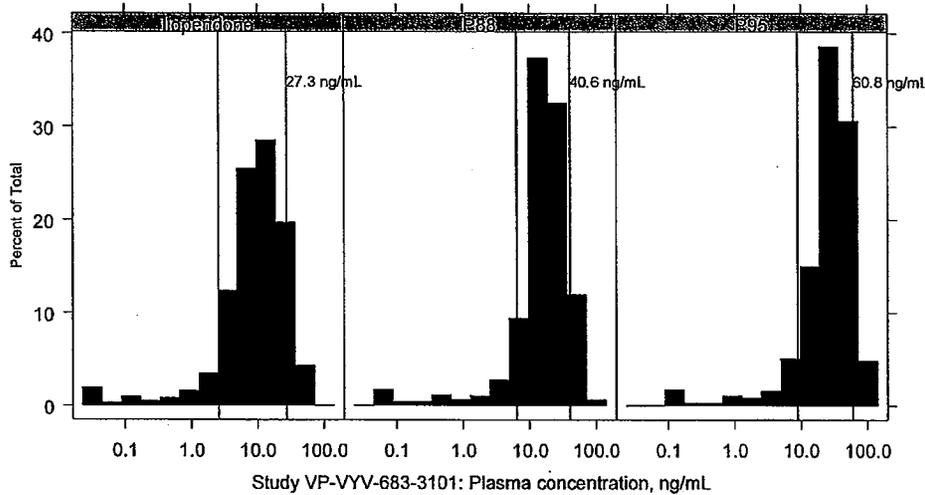
The inclusion of the three other antipsychotics served as reference points for the magnitude of observed QTc effects in this group of antipsychotic medications. Risperidone (8 mg daily) was initially included due to its reported limited effect on QTc (this treatment arm was removed by Amendment 2); quetiapine (750 mg daily) was included to represent the putative middle range of effect on QTc, and ziprasidone (160 mg daily) was included since it has the greatest reported effect on QTc among atypical antipsychotics. The doses of risperidone, quetiapine, and ziprasidone were based on recommendations from the manufacturers.

This study evaluated the effects of inhibition of both 3A4 and 2D6 in the iloperidone treatment arms by use of ketoconazole (200 mg b.i.d.) and paroxetine (20 mg q.d.), respectively. Ketoconazole was added as a metabolic inhibitor to the main P450 metabolic pathway of ziprasidone and quetiapine (CYP3A4).

*Reviewer's Comments:*

1. The iloperidone doses are acceptable. The 8mg BID, 12mg BID and 24 mg QD doses would cover the expected clinical exposures. Figure 1 illustrates distribution of iloperidone, P88 and P95 concentration in VP-VYU-683-310, a randomized, double-blind, placebo- and ziprasidone-controlled, multi-center clinical trial to evaluate the efficacy, safety and tolerability of a 24 mg/day dose iloperidone given b.i.d. for 28 days to schizophrenic patients in acute exacerbation followed by a long-term treatment phase.

**Figure 1: Distribution of Iloperidone, P88 and P95 concentrations in VP-VYU-683-3101, a phase 3 clinical trial, after 12mg BID (24 mg/day) dosing. The vertical line represent 10<sup>th</sup> and 90<sup>th</sup> percentile. The number corresponds to the 90<sup>th</sup> percentile concentration.**



2. From a dose perspective, administration of ziprasidone 80 mg b.i.d. is acceptable as an active control. According to the label, the highest recommended dose to be used in patients with schizophrenia is  QTc prolongation is expected with this dose; however, the magnitude of QTc effect is not well characterized.
3. From a dose perspective, administration of quetiapine 375 mg b.i.d. is acceptable as an active control. According to the label, efficacy in schizophrenia was demonstrated in a dose range of  wever, QTc prolongation is not well characterized.

b(4)

**4.2.5.3 Instructions with Regard to Meals**

Patients took all antipsychotic study medication in the morning at approximately 8:00 a.m., and in the evening at approximately 6:30 p.m. (except for patients receiving ILO 24 mg q.d., who received the morning dose only). All study medications were taken with food, except on those days described below.

On the days of ECG assessments (Days -2, -1, and 0, and Steady-State Days [SSD] 1, 2, and 3 of each treatment period), patients did not eat within 3 hours prior to, or during, the T<sub>MAX</sub> ECG assessments. Therefore, patients randomized to either iloperidone or risperidone did not eat breakfast (or ate breakfast only after morning ECGs were taken); those randomized to

ziprasidone did not eat lunch (or ate lunch only after afternoon ECGs were taken), in order to avoid the confounding effects of food on heart rate and QT duration around the  $T_{MAX}$  ECGs. Since blood concentrations of quetiapine are affected by food intake (maximum blood concentration achieved [ $C_{max}$ ] is increased with food intake) and ECGs recorded at  $T_{MAX}$  needed to be taken at 1, 1.5, and 2.5 hours after dosing, in order to maintain consistency of food restriction within 3 hours prior to the ECG recording, quetiapine was administered with a small, restricted, predefined liquid diet (e.g., Ensure®).

#### 4.2.5.4 ECG and PK Assessments

**Table 4: Assessment Schedule**

Phase		Treatment phase												
Period		Treatment Period 1 <sup>a</sup>				Treatment Period 2 <sup>b</sup>				Treatment Period 3 <sup>c</sup> (Iloperidone treated patients only)				
Evaluations	Day	D1 to DY <sup>d</sup>	SSD1	SSD2	SSD3	DX <sup>e</sup> -DY <sup>d</sup>	SSD1	SSD2	SSD3	DX <sup>e</sup> -DY <sup>d</sup>	SSD1	SSD2	SSD3	SC <sup>f</sup>
Meal Record			X	X	X		X	X	X		X	X	X	
Vital signs		Twice daily												
Electrocardiogram		X <sup>g</sup>	XXX	XXX	XXXXXXXXX	X <sup>g</sup>	XXX	XXX	XXX	X <sup>g</sup>	XXX	XXX	XXX	X
Laboratory evaluation, Physical exam, CGI-S														X
IVRS call														X <sup>h</sup>
Pharmacokinetic (PK) sample			X <sup>i</sup>	X <sup>i</sup>			X <sup>i</sup>	X <sup>i</sup>			X <sup>i</sup>	X <sup>i</sup>		
Pregnancy test, urine drug screen														X
Concomitant medications	Daily	X	X	X		X	X	X	X	X	X	X	X	X
Drug administration record (DAR)	Daily	X	X	X		X	X	X	X	X	X	X	X	X <sup>j</sup>
Adverse events (AEs), serious AEs (SAEs)	Daily	X	X	X		X	X	X	X	X	X	X	X	X
Study Completion (SC) form														X

<sup>a</sup> SSD1, 2, and 3 were the following study days for: ILO LOW=13,14,15; ILO HIGH=15, 16, 17; ILO QD=16, 17, 18; RIS=11, 12, 13; ZIP=8, 9, 10; QUET=10, 11, 12.

<sup>b</sup> Patients received one metabolic inhibitor in addition to the assigned treatment during this period: Iloperidone- and (prior to Amendment 2; see Section 4.1) risperidone-treated patients received paroxetine 20 mg q.d., and ziprasidone- and quetiapine-treated patients received ketoconazole 200 mg b.i.d. Note: Based on Amendment 2 (see Section 4.1.), the PM dose of ketoconazole was not given on the last day of study drug administration. SSD1, 2, and 3 are the following study days for: ILO LOW=21, 22, 23; ILO HIGH=23, 24, 25; ILO QD=24, 25, 26; RIS=19, 20, 21; ZIP=13, 14, 15; QUET=15, 16, 17.

<sup>c</sup> In addition to paroxetine, patients randomized to Iloperidone received ketoconazole 200 mg b.i.d. during this period. Patients randomized to any other treatment did NOT enter this period. During this period, SSD1, 2, and 3 were the following study days for: ILO LOW=26, 27, 28; ILO HIGH=28, 29, 30; ILO QD = 29, 30, 31.

<sup>d</sup> Day Y (DY) is the day immediately prior to SSD1 of this period. The corresponding study day is dependent on treatment assignment (see Tables 3-3 and 3-4).

<sup>e</sup> Day X (DX) is the day immediately following SSD3 of the prior period. The corresponding study day is dependent on treatment assignment (see Tables 3-3 and 3-4).

<sup>f</sup> SC=study completion evaluation conducted the morning following SSD3 of Period 2 or 3, depending on treatment assignment, or at premature discontinuation. Quetiapine, ziprasidone, and risperidone-treated patients had study completion evaluations performed the morning following SSD3 of Period 2. Iloperidone-treated patients had study completion performed the morning following SSD3 of period 3.

<sup>g</sup> One ECG was performed on the second day of each period (ILO HIGH=Days 2, 19, and 27; ILO LOW=Days 2, 17, 25; ILO QD=Days 2, 20, 28; and RIS=Days 2, 15; ZIP=Days 2, 12; QUET=Days 2, 14)

<sup>h</sup> The IVRS was called to report patient completion or discontinuation.

<sup>i</sup> 3 blood samples drawn from patients in the ILO group, 2 from patients in the ZIP, QUET, and (prior to Amendment 2; see Section 4.1) RIS groups.

<sup>j</sup> Three blood samples for pharmacokinetic analysis were drawn from patients in the Iloperidone group.

<sup>k</sup> Performed only at premature discontinuation.

(Source: Ilo522-2328-legacy report: Table 3-8, page 40)

#### 4.2.5.5 Baseline

The baseline QTc value was obtained by averaging all QTc values corresponding to the  $T_{max}$  of the compound on Days -2, -1, and 0.

#### 4.2.6 ECG Collection

Multiple ECG measurements were taken at baseline and during 3 consecutive days at the steady state of all drugs administered, and during steady state after adding metabolic inhibitor(s). Baseline and post-baseline ECG measurements were taken at the same time of the day. On the 3 consecutive days of Periods 1, 9 ECGs were collected to allow for evaluation of circadian variations. A central reader who was blind to patient randomization evaluated all ECGs using a manual high-resolution analysis of the ECG interval measurements.

The primary analysis compared 3 ECGs per day taken on each of 3 consecutive days at the  $T_{max}$  of the given compound to 3 ECGs per day taken on each of 3 consecutive days at baseline. A separate analysis was conducted to compare 3 ECGs per day taken on each of 3 consecutive days around the  $T_{MAX}$  after adding the selected metabolic inhibitor(s) of the given compound to 3 ECGs per day taken on each of 3 consecutive days at baseline. Additional ECG measurements were taken on Day 0 and Steady-State Day 3 of Period 1 in order to compare the change from baseline to endpoint of the specified antipsychotic medication on QTc throughout the day, without regard to the  $C_{max}$  of the compounds. In addition, ECGs were taken during medication titration for safety purposes, but were not used for purposes of analysis.

*Reviewer's Comment: ECG readers were only blinded to randomization. No triplicate ECGs were taken. ECGs were not sent to the ECG warehouse for review.*

## 4.2.7 Sponsor's Results

### 4.2.7.1 Study Subjects

The patient population for this study included patients who were diagnosed with schizophrenia or schizoaffective disorder but were not suffering from acute exacerbation of the disease. They were 18-65 years of age, 71-72% males in each group, with a normal baseline ECG.

Of the 188 randomized patients, eight withdrew before receiving study medication, and 180 patients received at least 1 dose of study medication. Of the 188 patients that were randomized, 149 completed the study (79%). Five patients were randomized to risperidone - this arm was removed following Amendment 2 of the protocol. The reasons for discontinuation in any group were treatment emergent AE's, treatment unsatisfactory, withdrawal of consent and protocol violation. Overall, 2 patients who received study medication were discontinued as a result of protocol violations; one patient was randomized to quetiapine 375 mg b.i.d. and one patient was randomized to risperidone 4 mg b.i.d. Additionally, 2 patients were discontinued for protocol violations before receiving study medication (both were randomized to iloperidone 8 mg b.i.d). Nine patients experienced AEs that lead to premature discontinuation. Of the 22 patients who withdrew consent, 19 belonged to the various iloperidone treatment groups.

*Reviewer's Comment: There were more discontinuations due to withdrawal of consent after receiving study treatment in the iloperidone groups.*

### 4.2.7.2 Statistical Analyses

#### 4.2.7.2.1 Primary Analysis

The sponsor's primary analysis compared 3 ECGs per day taken on each of 3 consecutive days at the  $T_{max}$  of the given compounds to 3 ECGs per day taken on each of 3 consecutive days at baseline. The primary variable of interest was the QTc change at  $T_{max}$  from baseline to steady state of treatment period 1. The baseline QTc value was obtained by averaging all QTc values corresponding to the  $T_{max}$  of the compound on Days -2, -1, and 0. The QTc value for the steady state was also averaged over all QTc values around  $T_{max}$  on Steady-State Day (SSD1), Steady-State Day 2 (SSD2), and Steady-State Day 3 (SSD3) of treatment period 1. The primary analysis used the Fridericia's method to correct the QT duration for heart rate.

The primary variable was analyzed by an ANCOVA model with adjusted baseline QTC value as a covariate and treatment and gender as class variables. The adjusted baseline QTc value for

each patient was obtained by subtracting the mean of all original baseline values around  $T_{max}$  for all patients from that patient's baseline QTc value.

The primary QTc population for the QTc analysis were all patients who had at least 50% ( $\geq 5$ ) of the QTc evaluations on days SSD1, SSD2, and SSD3 at  $T_{max}$  during treatment period 1 and at least half ( $\geq 5$ ) of the QTc evaluations around times that corresponded to the  $T_{max}$  for each compound at baseline (Days -2, -1, and 0).

The sponsor's primary analysis is presented in Table 5. The table reported the raw means (unadjusted for covariates) as well as the least square means. The least square means are based on the ANCOVA model with adjusted baseline QTc as a covariate, gender and treatment as factors. The least square means did not differ substantially from the raw means.

**Table 5. Summary statistics of QTcF (Fridericia correction) change (95% CI) from baseline to steady state at  $T_{max}$  during Treatment Period 1 (Primary QTc population)**

	Ilo 8 mg	Ilo 12 mg	Ilo 24 mg	Zip	Quet
<i>Sample size</i>	28	34	31	32	33
<i>Baseline</i>					
Raw mean $\pm$ SD	385.9 $\pm$ 16.4	386.5 $\pm$ 17.1	379.0 $\pm$ 14.7	383.4 $\pm$ 13.5	383.2 $\pm$ 18.9
<i>Change in QTcF</i>					
Raw mean $\pm$ SD	8.5 $\pm$ 10.5	9.0 $\pm$ 12.5	15.4 $\pm$ 11.7	9.6 $\pm$ 11.0	1.3 $\pm$ 11.1
LS mean*	9.1	9.7	14.6	9.7	1.3
(95% CI for LS mean)	(4.9, 13.3)	(5.8, 13.6)	(10.6, 18.9)	(5.7, 13.7)	(-2.5, 5.2)

\* The least square means and confidence intervals are provided by the reviewer. The model included risperidone group that was dropped according to Protocol Amendment 2. These results are slightly different than the results reported on Table 9.2.1-2, page 308 as the sponsor's results included two additional patients from the secondary QTc population)

(Source: Ilo522-2328-legacy report: Table 9-1, page 57)

#### 4.2.7.2.2 Categorical Analysis

No patient experienced a QTc of  $\geq 500$  ms during the study. Number of patients with QTc increase from baseline to steady state at  $T_{max}$  of  $\geq 30$  and 60 ms during treatment periods 1, 2, and 3 are presented in Table 6

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**Table 6. Number (%) of Patients with QTc Increase from baseline to Steady-State at T<sub>max</sub> of ≥ 30 and 60 ms during Treatment Periods 1, 2, and 3**

	ILO 8 mg b.i.d.		ILO 12 mg b.i.d.		ILO 24 mg q.d.		ZIP 80 mg b.i.d.		QUET 375 mg b.i.d.	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
<b>Treatment Period 1</b>										
<b>Increase ≥ 30 msec</b>										
Fridericia	29	9 (31)	34	15 (44)	31	19 (61)	33	17 (52)	33	4 (12)
Baseline	29	9 (31)	34	15 (44)	31	19 (61)	33	14 (42)	33	5 (15)
FDA	29	11 (38)	34	15 (44)	31	21 (68)	33	15 (45)	33	7 (21)
Bazett	29	21 (72)	34	21 (62)	31	26 (84)	33	20 (61)	33	18 (55)
<b>Increase ≥ 60 msec</b>										
Fridericia	29	1 (3)	34	0 (0)	31	1 (3)	33	0 (0)	33	0 (0)
Baseline	29	1 (3)	34	0 (0)	31	1 (3)	33	0 (0)	33	0 (0)
FDA	29	1 (3)	34	1 (3)	31	1 (3)	33	0 (0)	33	0 (0)
Bazett	29	1 (3)	34	3 (9)	31	4 (13)	33	5 (15)	33	1 (3)
<b>Treatment Period 2</b>										
<b>Increase ≥ 30 msec</b>										
Fridericia	26	14 (54)	31	15 (48)	31	22 (71)	30	18 (60)	32	6 (19)
Baseline	26	13 (50)	31	15 (48)	31	22 (71)	30	19 (63)	32	6 (19)
FDA	26	14 (54)	31	13 (42)	31	22 (71)	30	19 (63)	32	7 (22)
Bazett	26	17 (65)	31	13 (42)	31	21 (68)	30	23 (77)	32	21 (66)
<b>Increase ≥ 60 msec</b>										
Fridericia	26	1 (4)	31	0 (0)	31	1 (3)	30	0 (0)	32	0 (0)
Baseline	26	1 (4)	31	0 (0)	31	1 (3)	30	0 (0)	32	0 (0)
FDA	26	1 (4)	31	0 (0)	31	0 (0)	30	0 (0)	32	0 (0)
Bazett	26	0 (0)	31	1 (3)	31	1 (3)	30	1 (3)	32	3 (9)
<b>Treatment Period 3</b>										
<b>Increase ≥ 30 msec</b>										
Fridericia	25	13 (52)	30	21 (70)	29	20 (69)	—	—	—	—
Baseline	25	14 (56)	30	20 (67)	29	19 (66)	—	—	—	—
FDA	25	14 (56)	30	20 (67)	29	19 (66)	—	—	—	—
Bazett	25	14 (56)	30	20 (67)	29	19 (66)	—	—	—	—
<b>Increase ≥ 60 msec</b>										
Fridericia	25	1 (4)	30	3 (10)	29	0 (0)	—	—	—	—
Baseline	25	1 (4)	30	3 (10)	29	0 (0)	—	—	—	—
FDA	25	1 (4)	30	3 (10)	29	0 (0)	—	—	—	—
Bazett	25	2 (8)	30	5 (17)	29	1 (3)	—	—	—	—

N=number of patients; ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine  
 \*T<sub>max</sub>=estimated time of maximum concentration (ILO=2-4 hours post-dose;  
 ZIP=5-7 hours post-dose; QUET=1-2.5 hours post-dose).  
 Each patient is counted once within each steady state if he/she had at least one QTc increase ≥30 msec or ≥60 msec from baseline.

(Source: Ilo522-2328-legacy report: Table 9-3, page 63)

#### 4.2.7.2.3 Additional Analyses

The primary analysis was in period 1 (no additional inhibitors). Additional analyses for periods 2 and 3 were performed and the results are presented in Table 7. In comparison to treatment period 1, the mean change from baseline in QTcF (Fridericia correction) at T<sub>max</sub> was numerically higher in all treatment groups for treatment period 2 and in iloperidone groups for treatment period 3.

**Table 7. Summary statistics of QTcF change (95% CI) from baseline to steady state at Tmax during Treatment Periods 1, 2, and 3 (Primary QTc population)**

	Ilo 8 mg	Ilo 12 mg	Ilo 24 mg	Zip	Quet
<b>Period 1</b>					
<i>Sample size</i>	28	34	31	32	33
<i>Baseline</i>					
Raw mean ± SD	385.9 ± 16.4	386.5 ± 17.1	379.0 ± 14.7	383.4 ± 13.5	383.2 ± 18.9
<i>Change in QTcF</i>					
Raw mean ± SD	8.5 ± 10.5	9.0 ± 12.5	15.4 ± 11.7	9.6 ± 11.0	1.3 ± 11.1
LS mean*	9.1	9.7	14.6	9.7	1.3
(95% CI for LS mean)	(4.9, 13.3)	(5.8, 13.6)	(10.6, 18.9)	(5.7, 13.7)	(-2.5, 5.2)
<b>Period 2</b>					
<i>Sample size</i>	26	31	31	30	32
<i>Baseline</i>					
Raw mean ± SD	387.3 ± 16.1	386.1 ± 17.7	379.0 ± 14.7	383.0 ± 13.2	382.8 ± 19.1
<i>Change in QTcF</i>					
Raw mean ± SD	11.2 ± 12.0	11.6 ± 16.8	17.5 ± 10.3	15.9 ± 11.8	2.6 ± 11.5
LS mean	11.9	11.9	16.0	15.4	2.1
(95% CI for LS mean)	(7.2, 16.6)	(7.6, 16.3)	(11.7, 20.3)	(11.1, 19.8)	(-2.1, 6.3)
<b>Period 3</b>					
<i>Sample size</i>	25	30	29	--	--
<i>Baseline</i>					
Raw mean ± SD	387.5 ± 16.4	384.5 ± 15.6	379.6 ± 14.9	--	--
<i>Change in QTcF</i>					
Raw mean ± SD	15.7 ± 14.1	19.3 ± 17.1	19.5 ± 11.9	--	--
LS mean	15.8	18.5	17.6	--	--
(95% CI for LS mean)	(10.1, 21.6)	(13.2, 23.9)	(12.3, 22.9)	--	--

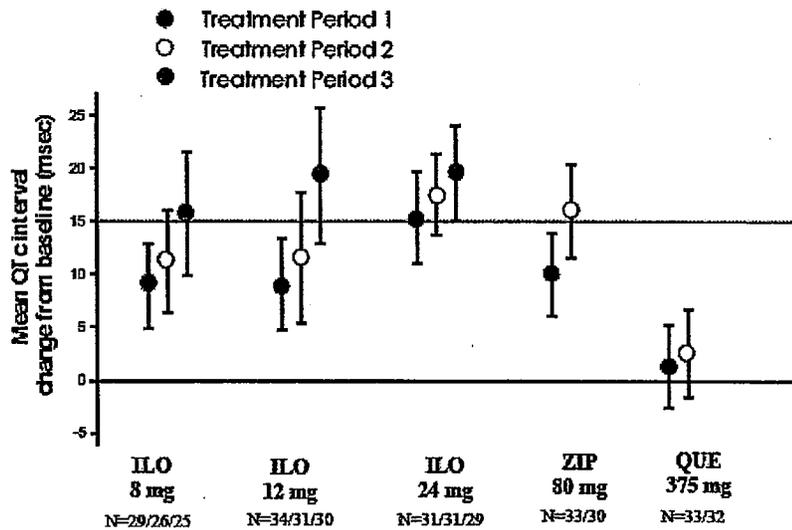
\* The least square means and confidence intervals for Period 1 are provided by the reviewer. These results are slightly different than the results reported on Table 9.2.1-2, page 308 as the sponsor's results included two additional patients from the secondary QTc population)

(Source: Ilo522-2328-legacy report: Table 9-2, page 60, Table 9.2.1-2, pages 309-310)

*Reviewer's Comments: The results produced by the sponsor were based on 2-sided 95% CI. We calculated 2-sided 90% CI for our analysis.*

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**Figure 2: Mean QTcF Change from Baseline to Steady State T<sub>max</sub> during Treatment Periods 1, 2, and 3**



ILO=iloperidone; ZIP=ziprasidone; QUE=quetiapine  
 P1=Period 1, P2=Period 2, P3=Period 3  
 Note: \* T<sub>max</sub> = estimated time of maximum concentration (ILO=2-4 hours post-dose; ZIP=5-7 hours post-dose;  
 QUET= 1-2.5 hours post-dose)  
 Source: Figure 9.2-1

(Source: Ilo522-2328-legacy report: Figure 9-2, page 61)

#### 4.2.7.3 Safety Analysis

There were *no deaths* in this study.

- Three patients experienced a serious adverse event (SAEs) during treatment with study medication. One 38 yr old male randomized to the iloperidone 8 mg b.i.d. group experienced a run of severe supraventricular tachycardia (>200bpm) on day 7 which responded to cardizem. The patient was discontinued from study drug and switched to olanzapine. A 47 yr old female, randomized to iloperidone 24 mg q.d. experienced new onset uncontrolled DM 11 days after study drug. The other SAE was aggravated psychosis on quetiapine
- Additionally, one patient experienced a SAE (altered mental status and brief psychotic reaction) before randomization, and one patient experienced a SAE (pain in extremities and shortness of breath) after study medication (iloperidone 8 mg b.i.d.) was discontinued.
- There were nine discontinuations due to AEs (6 from the various iloperidone groups). A 49 yr old male randomized to ILO 12 mg b.i.d. experienced mild sinus bradycardia on Study Day 19 and moderate hypotension on Study Day 25. On Study Day 30 the patient experienced moderate presyncope and sinus bradycardia (60 and 58 bpm, morning and evening measurements respectively). The patient did not receive any further treatment for the sinus bradycardia and was withdrawn from the study. His pulse was within normal ranges by the following day. Another 43 yr old male

- experienced ongoing intermittent tachycardia (reported as tachycardia NOS) on iloperidone 24 mg q.d. and was discontinued from study drug on day 27.
- 15 patients experienced cardiac AEs- of these 12 were from the iloperidone group. Ten were reported as tachycardia NOS. The other two events were supraventricular tachycardia and sinus bradycardia as described above.
  - The most common (>10%) treatment-emergent AEs for iloperidone-treated patients included headache, anxiety, dyspepsia, insomnia, dizziness, constipation, tachycardia, diarrhea, EPS, fatigue, dry mouth, nasal congestion, somnolence, akathisia, cough, sedation, and pharyngitis.

#### 4.2.7.4 Clinical Pharmacology

##### 4.2.7.4.1 Pharmacokinetic Analysis

Average peak concentrations (average of concentrations on steady-state days 1 and 2) and mean peak concentration ratios in the presence vs. the absence of metabolic inhibitors are presented in Table 8.

- Compared with peak steady-state concentration of iloperidone in the absence of inhibition (Period 1), mean peak concentrations in the presence of paroxetine (Period 2) increased 29-64%, with the lowest percentage increase in the iloperidone 24 mg q.d. group and the highest in the iloperidone 8 mg b.i.d.
- The increases in the iloperidone concentrations in the presence of paroxetine and ketoconazole (Period 3) were 54-134%, with lowest percentage increase in the iloperidone 24 mg q.d. group and the highest in the iloperidone 8 mg b.i.d.
- For the primary active metabolite of iloperidone, P88, the corresponding increases in concentrations were comparable or slightly larger, i.e. 29-73% in Period 2, and 84-171% in Period 3.
- For iloperidone metabolite P95 (non-active), mean peak concentrations reduced to ~50% in Period 2 and to ~30% in Period 3, compared to the peak concentration levels without metabolic inhibition in Period 1. Mean peak concentration increases due to metabolic inhibitor ketoconazole were 24%, and 334% for ziprasidone, and quetiapine respectively.

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**Table 8: Average Peak Concentrations and Ratios of Average Peak Concentrations in the Presence and in the Absence of Metabolic Inhibitors**

Analyte	Average Peak Concentration						Ratio			Ratio		
	Period 1 <sup>b</sup>		Period 2 <sup>b</sup>		Period 3 <sup>b</sup>		(periods 2/1)			(periods 3/1)		
	Mean	CV <sup>c</sup>	Mean	CV	Mean	CV	Mean	N	CV	Mean	N	CV
Iloperidone												
Ilo 8 mg bid	12.35	57	19.00	53	25.62	42	1.64	25	30	2.34	24	33
Ilo 12 mg bid	20.88	43	32.20	44	47.43	55	1.60	31	41	2.29	30	43
Ilo 24 mg qd	29.47	39	36.01	56	46.56	41	1.29	29	62	1.54	26	38
P88												
Ilo 8 mg bid	18.03	52	28.77	36	44.92	32	1.73	25	35	2.71	24	39
Ilo 12 mg bid	24.44	37	36.84	28	54.55	38	1.57	31	25	2.31	30	32
Ilo 24 mg qd	33.12	45	39.77	40	60.10	50	1.29	29	37	1.84	27	39
P95												
Ilo 8 mg bid	33.39	62	15.15	48	11.01	67	0.50	25	41	0.35	24	62
Ilo 12 mg bid	47.22	53	20.83	48	15.89	89	0.52	31	49	0.31	30	50
Ilo 24 mg qd	54.59	50	20.43	58	14.44	103	0.43	29	78	0.25	27	78
Ziprasidone	168.27	43	211.91	41	-	-	1.33	28	47	-	-	-
Quetiapine	825.95	61	2146.8	39	-	-	4.34	31	110	-	-	-

Note: (a) Average of peak concentrations at steady-state day 1 and day 2. (b) Period 1: no inhibition, Period 2: add one inhibitor, and Period 3: add two inhibitors. (c) CV: coefficient of variation in %.

(Source: Ilo522-2328-legacy report: Table 9-4, page 65)

#### 4.2.7.4.2 Exposure-Response Analysis

Linear models were used to assess the effects of concentrations on mean QTc change. The primary QTc variable in the analysis was the average QTc of three measurements obtained at the T<sub>max</sub> (one on each of the three steady-state days during the treatment periods). The timing of the QTc measurements was compound-dependent as they were collected at the T<sub>max</sub> for each compound. The QTcs measured at the corresponding timepoints during the three days prior to treatment were averaged similarly, and were defined as baseline QTcs. Mean QTc change was the difference between the mean QTc during treatment and the mean QTc at baseline.

Mean QTc change from baseline at T<sub>max</sub> in each treatment period was the dependent variable. The independent variables included the corresponding mean QTc at baseline, and concentrations (parent and metabolites) at their T<sub>max</sub>. Concentrations were centered at the sample mean in each treatment period, and scaled by ~ 1/2 standard deviation, i.e. 10 ng/mL for iloperidone and metabolites, 50 ng/mL for ziprasidone, and 500 ng/mL for quetiapine. Baseline mean QTc was centered at 385 ms and scaled by 10 ms. The parameters in the model were intercept, slope for baseline QTc term, and slope for concentration term. The intercept represented the average QTc change for a patient whose drug concentration was at the centered concentration value and whose baseline QTc was at 385 ms. The slope for the concentration term measured the concentration effect on QTc change. A positive slope indicated an increase in QTc change as concentration increased by the magnitude of the scaled concentration, e.g. 10 ng/mL for iloperidone, P88 and P95, 50 ng/mL for ziprasidone and 500 ng/mL for quetiapine. The slope of the QTc term was interpreted similarly as the effect on QTc change per 10 ms increase in the baseline QTc. Analyses were carried for each analyte in each treatment period.

The intercept and slopes (for both baseline QTc and peak concentration of the analyte) together with the centered sample mean concentrations are presented in Table 9.

The QTc change in the presence of inhibition (Periods 2 and 3) was larger, compare to the QTc change in the absence of inhibition (Period 1). Baseline QTc was an important factor in the change of QTc, and greater QTc baseline was associated with lower change in QTc. For iloperidone treated patients, a 10 ms increase in baseline QTc resulted in a 2-4 ms reduction in QTc change regardless the presence of metabolic inhibition. Within treatment period, QTc change tended to increase with concentrations of iloperidone and its metabolite P88 for iloperidone treated patients. The concentration effects were significant for iloperidone at Period 2 and for P88 at Period 2 and 3 ( $p < 0.02$ ). For ziprasidone and quetiapine, larger QTc changes and higher drug concentrations were associated with metabolic inhibition. The effects of baseline QTc on QTc change was similar to that in the iloperidone treated patients. None of the concentration effect on QTc change within treatment period was significant ( $p = 0.3861$ ).

**Table 9: Modeling the Effect of Drug and Metabolites Concentrations on the Mean QTc Change at T<sub>max</sub>**

Analyte	Term	Period 1			Period 2			Period 3		
		Est	S.E.	p-val <sup>b</sup>	Est	S.E.	p-val	Est	S.E.	p-val
Ilo	Intercept <sup>a</sup>	11.34	1.44	<.0001	13.35	1.50	<.0001	18.66	1.64	<.0001
	Slope 1 <sup>a</sup>	-2.17	0.87	.0148	-3.70	0.91	<.0001	-2.78	1.04	.0089
	Slope 2 <sup>a</sup>	1.66	1.30	.2059	2.54	0.91	.0063	1.30	0.74	.0845
	C <sub>MEAN</sub> <sup>a</sup>	21.00			29.59			40.00		
	N <sup>a</sup>	91			88			84		
P88	Intercept	10.42	1.42	<.0001	13.14	1.38	<.0001	17.76	1.52	<.0001
	Slope 1	-3.48	0.88	.0001	-3.34	0.83	.0001	-2.91	0.98	.0041
	Slope 2	1.39	1.16	.2312	2.64	1.05	.0135	2.63	0.68	.0002
	C <sub>MEAN</sub>	25.23			36.23			54.65		
	N	91			88			84		
P95	Intercept	10.40	1.43	<.0001	13.12	1.43	<.0001	17.63	1.65	<.0001
	Slope 1	-3.68	0.85	<.0001	-3.75	0.84	<.0001	-4.21	1.00	<.0001
	Slope 2	0.54	0.56	.3340	1.30	1.39	.3530	1.03	1.28	.4251
	C <sub>MEAN</sub>	45.31			19.14			14.10		
	N	91			88			84		
Zip	Intercept	6.50	1.76	.0009	14.29	2.26	<.0001	-	-	-
	Slope 1	-2.27	1.36	.1052	-2.53	1.71	.1505	-	-	-
	Slope 2	-0.04	1.27	.9758	0.79	1.15	.4982	-	-	-
	C <sub>MEAN</sub>	168			198			-	-	-
	N	33			30			-	-	-
Que	Intercept	1.72	2.05	.4093	3.37	2.39	.1705	-	-	-
	Slope 1	-2.39	1.05	.0301	-3.37	1.19	.0084	-	-	-
	Slope 2	1.79	2.03	.3861	1.21	1.44	.4051	-	-	-
	C <sub>MEAN</sub>	826			2147			-	-	-
	N	33			31			-	-	-

Note: (a) The units for Intercept is msec. The unit of Slope 1 (the slope of the baseline QTc term) is msec/(10 msec of baseline QTc). The units of Slope 2 (the slope of the analyte concentration term) are msec/(10 ng/mL) for iloperidone and its metabolites, msec/(50 ng/mL) for ziprasidone, and msec/(500 ng/mL) for quetiapine. C<sub>MEAN</sub> is the centered mean concentration in the treatment period. N: number of patients. (b) p-values were based on Wald's test and referred to the null hypothesis that the term equals zero.

(Source: Ilo522-2328-legacy report: Table 9-5, page 67)

*Reviewer's Comments: The effect of iloperidone and its metabolites on QTc appears to be concentration dependent. The exposure-response analysis by the sponsor was not thoroughly reviewed. The reviewer's also did not conduct exposure-response analyses for iloperidone due to assay sensitivity issues (see clinical pharmacology reviewer's analyses)*

## 5 REVIEWERS' ASSESSMENT

### 5.1 STATISTICAL ASSESSMENTS

This study was not a placebo-controlled study. Active therapies (ziprasidone and quetiapine) were used as references. However, no direct comparison between iloperidone and ziprasidone/quetiapine was performed. The drugs were also administered open-label. Thus, the study is subject to potential bias.

In the sponsor's primary analysis, the baseline QTc measurements were averaged over three baseline days around the  $T_{max}$  and the endpoint QTc measurements were averaged over three steady-state days around the  $T_{max}$ . Because the study was not designed for a time-matched analysis, the following analysis is only to mimic the E-14 analysis. The endpoint QTc measurements were the 9 measurements taken over 9 time points on Steady-State Day 3. The baseline QTc measurements were the 9 measurements taken over 9 time points on Baseline Day 0. At each timepoint, an ANCOVA model was utilized with gender and treatment group as factors and an adjusted baseline QTc measurement as a covariate. The adjusted baseline was computed by subtracting the average baseline from each patient's baseline measurement.

For iloperidone 12 mg, iloperidone 24 mg, and quetiapine, the largest effect on the QTcF occurs in the morning. For iloperidone 8 mg and ziprasidone, the largest effect occurs in the afternoon and late afternoon.

These results along with the primary results suggest that iloperidone (8 mg – 24 mg) is associated with a prolongation of the QT interval above the threshold established by the ICH-E14 guidance.

**Table 10. Time-matched analysis of QTc (Fridericia correction) change (90% CI) from baseline (Day 0) to steady state (Day SSD3) during Treatment Period 1 (Primary QTc population)**

	Ilo 8 mg	Ilo 12 mg	Ilo 24 mg	Zip	Quet
sample size	28	34	31	32	33
Time 1	10.1 (4.8, 15.4)	9.0 (4.0, 14.0)	14.7 (9.6, 19.8)	6.0 (0.9, 11.1)	3.5 (-1.5, 8.5)
Time 2	8.9 (3.2, 14.6)	8.2 (3.0, 13.4)	16.8 (11.4, 22.2)	7.6 (2.2, 13.0)	5.1 (-0.2, 10.4)
Time 3	6.6 (1.5, 11.7)	11.8 (7.1, 16.5)	14.1 (9.1, 19.1)	8.8 (4.0, 13.6)	2.2 (-2.6, 7.0)
Time 4	11.1 (6.0, 16.2)	7.1 (2.4, 11.8)	10.8 (5.9, 15.7)	6.1 (1.2, 11.0)	0.2 (-4.6, 5.0)
Time 5	10.5 (5.0, 16.0)	7.8 (2.9, 12.7)	6.6 (1.5, 11.7)	6.9 (1.8, 12.0)	-0.8 (-5.8, 4.2)
Time 6	6.3 (1.4, 11.2)	8.5 (4.1, 12.9)	7.6 (3.0, 12.2)	12.9 (8.3, 17.5)	5.2 (0.7, 9.7)
Time 7	8.5 (4.0, 13.0)	7.5 (3.4, 11.6)	3.9 (-0.3, 8.1)	11.6 (7.4, 15.8)	-1.3 (-5.4, 2.8)
Time 8	5.5 (0.6, 10.4)	8.5 (4.1, 12.9)	5.0 (0.4, 9.6)	3.6 (-1.0, 8.2)	-0.6 (-5.1, 3.9)
Time 9	5.2 (0.0, 10.4)	7.1 (2.3, 11.9)	2.5 (-2.4, 7.4)	4.4 (-0.5, 9.3)	-1.2 (-6.0, 3.6)

(Source: Reviewer's results)

## 5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

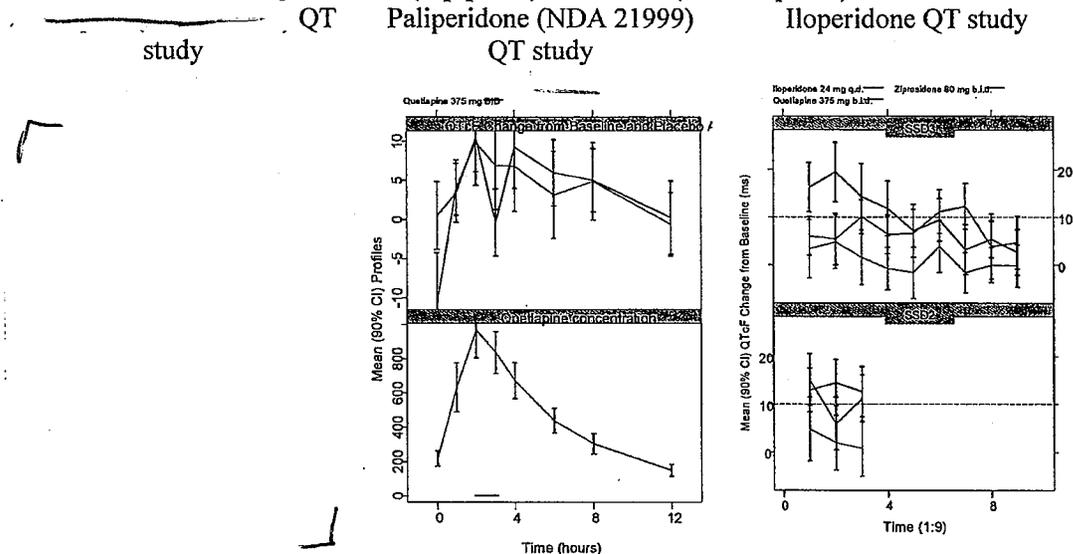
### 5.2.1 Assay Sensitivity

Using the quetiapine as the positive control, assay sensitivity could not be established. Based on the exposure-response analysis from TQT studies submitted to [redacted] and NDA 21999 for paliperidone, quetiapine is expected to prolong QTc ~10 ms at mean concentration of 1000 ng/mL. In this study, quetiapine exposures in period 1 (mean  $C_{max}$  825 ng/mL) and period 2 (mean  $C_{max}$  2146 ng/mL) are expected to exhibit QTc prolongation ~10 ms. However, none of the periods resulted in such effects on QTc (see Figure 3).

Additionally, the time-course of  $\Delta$ QTc closely followed plasma quetiapine concentration-time profile in [redacted] and paliperidone studies. No such time course was seen on any of the days in the current study. Figure 3 shows time course of change in QTc from baseline on days SSD2 and SSD3. Note that there were no pharmacokinetic samples available on SSD3. There are two possible reasons for such behavior in QT studies (1) absence of assay sensitivity due to poor study conduct or (2) inability to correct for placebo effect as the study did not include concurrent placebo arm.

Due to inherent limitation in study design, limited data were available for exposure response analyses. From quetiapine treated group, only 130 time matched concentration- $\Delta$ QTcF observations were available. Given the absence of placebo data and lack of time course in effect on QTc, the decision was made no to conduct exposure response analyses for quetiapine.

**Figure 3: Mean  $\Delta$ QTcF (upper panel) and quetiapine (bottom panel) concentration-time profile from [redacted] and paliperidone studies.  $\Delta$ QTcF-time profiles from iloperidone study on SSD3 (top panel) and SSD2 (bottom panel)**



(Source: Reviewer's results)

b(4)

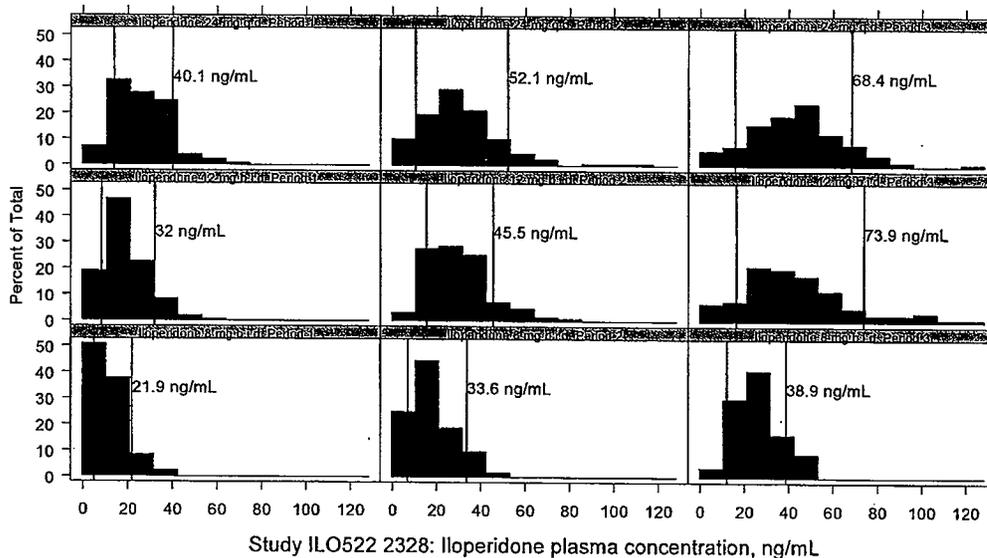
### 5.2.2 Exposure-Response Analyses for Iloperidone

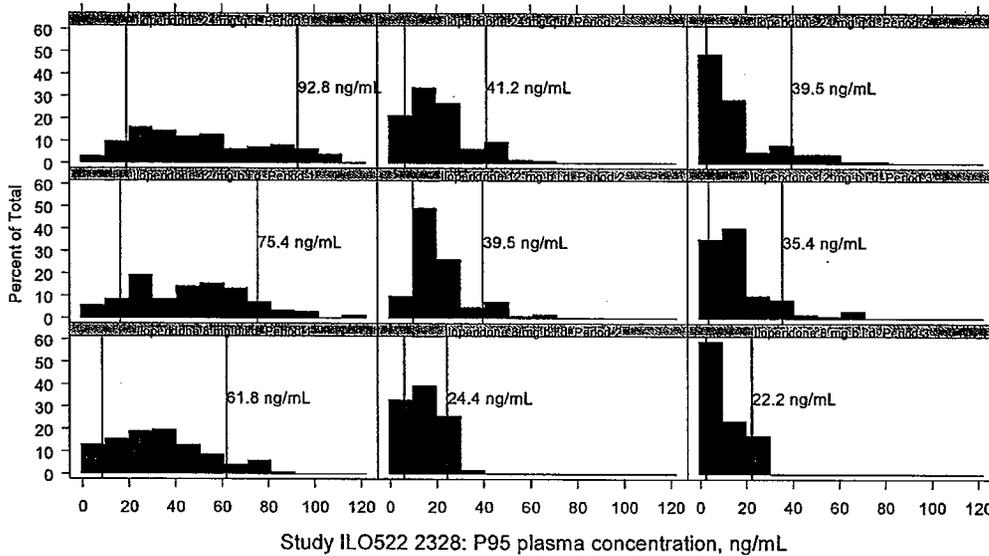
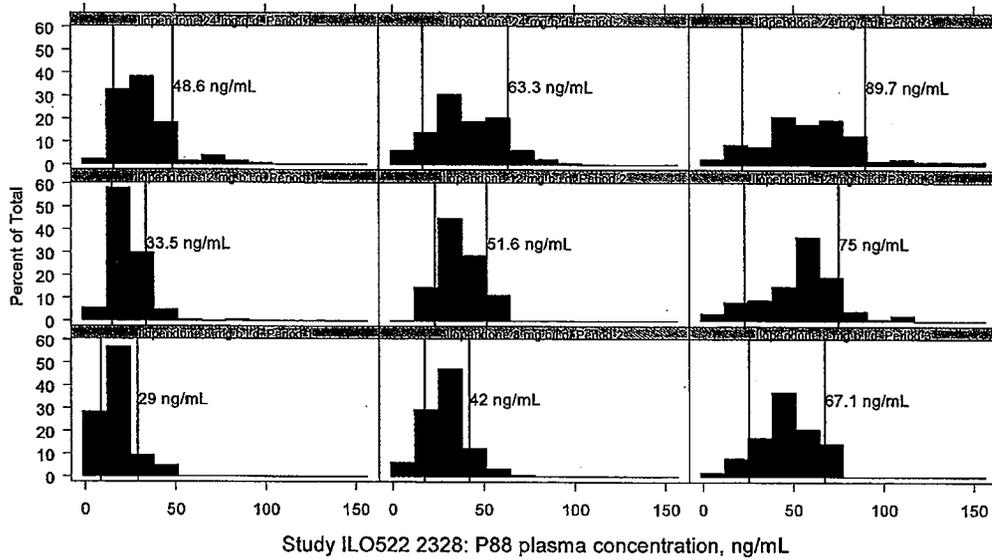
Since the assay sensitivity cannot be established, the reviewer did not conduct exposure-response analyses for iloperidone.

### 5.2.3 Dose Evaluation

Pharmacokinetic data were available from study VP-VYV-683-3101, a randomized, double-blind, placebo- and ziprasidone-controlled, multi-center clinical trial to evaluate the efficacy, safety and tolerability of a 24 mg/day dose iloperidone given b.i.d. for 28 days to schizophrenic patients in acute exacerbation followed by a long-term treatment phase. The short-term double-blind phase consisted of a 7-day fixed titration period followed by a 21-day dosing period. Iloperidone was provided as an over-encapsulated tablet containing 1, 2, 4, 6, 8, 10, or 12 mg. Blood samples for analysis of plasma concentrations of iloperidone were collected on Days 7, 14, 21 and 28 (or at the time of premature discontinuation). Figure 1 illustrates distribution of iloperidone, P88 and P95 concentration in VP-VYU-683-3101. The observed 90<sup>th</sup> percentiles were 27.3, 40.6 and 60.8 ng/mL, respectively. Figure 4 illustrates distribution of iloperidone, P88 and P95 concentration in ILO522 2328. The concentrations achieved in the QT study reasonably cover therapeutic concentration range at 24mg/day (12mg BID) clinical dose or lower.

**Figure 4: Distribution of Iloperidone, P88 and P95 concentrations in ILO522 2328 after 3 doses. The vertical line represent 10<sup>th</sup> and 90<sup>th</sup> percentile. The number corresponds to the 90<sup>th</sup> percentile concentration.**





### 5.3 CLINICAL ASSESSMENTS

None of the clinical events identified to be of particular importance per the ICH E14 guidelines (i.e. death, seizures, syncope and significant ventricular arrhythmias) were reported in this study. However, one patient experienced sinus bradycardia and presyncope. Another patient had supraventricular tachycardia reported as a SAE. Tachycardia NOS occurred more frequently in the iloperidone treatment groups.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Iloperidone efficacy has been established in the dose range of 4-24 mg/day. The recommended target dosage of iloperidone is 12 mg/day administered BID. The recommended titration schedule to target dose is 1, 2, 4, 6 mg BID on days 1, 2, 3, and 4 respectively. After reaching the target 12 mg/day dose, titration to the maximum daily dose of 12 mg BID (24 mg/day) should occur over a 3-day period.	
Maximum tolerated dose	Healthy volunteers: 3 mg (ILPB101)  No MTD studies were performed in patients with schizophrenia. It is believed that the MTD has not been reached when up to 32 mg/d was administered to patients with schizophrenia (ILPB203).	
Principal adverse events	In healthy volunteers, the AEs that lead to the declaration of the MTD were the following: dysphoria, dizziness, hypotension, tachycardia, lethargy, nausea and drowsiness (ILPB101)	
Maximum dose tested	Single Dose	Without PK: 32 mg (ILPB203) With PK: 24 mg QD (ILO522 2328)
	Multiple Dose	12 mg BID (ILO522 0112)
Exposures Achieved at Maximum Tested Dose	Single Dose	mean (%CV) $C_{max}$ : 29.47 (39) ng/mL (ILO522 2328) AUC: not determined
	Multiple Dose	mean (%CV) $C_{max}$ : 32.14 (43) ng/mL (ILO522 0112) AUC: 231.9 (48) ng*hr/mL.
Range of linear PK	Iloperidone and its metabolites, P88 and P95, show dose proportionality at steady-state in patients with schizophrenia over the dose range of 2 to 12 mg BID. (ILO522 0112).	
Accumulation at steady state	Considering that $C_{max}$ of iloperidone after a single dose of 3 mg was in the order of 3 ng/mL, the steady-state $C_{max}$ of iloperidone at the 12 mg BID dose was 32.14 ng/mL (ILO522 0112), and assuming dose-proportionality, accumulation of iloperidone with multiple BID dosing appears to be at least two-fold.	
Metabolites	There are two major iloperidone metabolites: <ul style="list-style-type: none"> <li>• P88 – has similar receptor binding profile as iloperidone and crosses the blood-brain barrier</li> <li>• P95 – has different receptor binding profile as iloperidone and does not cross the blood-brain barrier, therefore considered “centrally” inactive</li> </ul>	
Absorption	Absolute/Relative Bioavailability	Iloperidone absorption was at least 56% of a 3 mg [ $^{14}$ C]iloperidone dose given to normal healthy volunteers (ILO522 2301).

		An absolute bioavailability (BA) study was not performed. Absolute bioavailability is roughly estimated to be about 36% in CYP2D6 extensive metabolizers (EM) and about 54% in CYP2D6 poor metabolizers (PM), which is compatible with first-pass effect being smaller in PM due to lower CYP2D6 activity (ILO522 2301).
	Tmax	<ul style="list-style-type: none"> <li>• Iloperidone: 1.5-1.8 (0.75-8.0) h</li> <li>• P88: 2.5-3.0 (0.75-8.0) h</li> <li>• P95: 2.5-2.8 (1-12) h (ILO522 0112)</li> </ul>
Distribution	Vd/F or Vd	<p><u>V<sub>d</sub>/F</u> (ILO522 2301)</p> <ul style="list-style-type: none"> <li>• 2000 L in CYP2D6 extensive metabolizers (EM)</li> <li>• 1310 L in CYP2D6 poor metabolizers (PM)</li> </ul>
	% bound	Plasma protein binding of iloperidone is about 95% and is similar in man and in laboratory animals. Protein binding was unchanged in subjects with renal impairment (ILO522 0102), hepatic impairment (ILO522 0103) and in the presence of ketoconazole in blood (ILO522 0107).
Elimination	Route	The main route of elimination in humans is urine (70% of the dose in CYP2D6 extensive metabolizers (EM), 61% in CYP2D6 poor metabolizers (PM)), with biliary excretion to feces contributing a minor portion (21% in CYP2D6 EM, 25% in CYP2D6 PM). (ILO522 2301)
	Terminal t½	<ul style="list-style-type: none"> <li>• Iloperidone: 19.0/19.5 h (EM/PM)</li> <li>• P88: 23.2/12.7 h (EM/PM)</li> <li>• P95: 25.8/23.0 h (EM/PM) (ILO522 2301)</li> </ul>
	CL/F or CL	<p><u>CL/F</u> (ILO522 2301)</p> <ul style="list-style-type: none"> <li>• 102 L/h in CYP2D6 extensive metabolizers (EM)</li> <li>• 47.7 L/h in CYP2D6 poor metabolizers (PM)</li> </ul>
Intrinsic Factors	Age	No specific study was conducted to evaluate the effect of age. In the Phase 2 efficacy and safety study ILP2001,

		<p>plasma iloperidone concentrations predicted from a PK model were found not to correlate with age. Similarly, in the population PK analysis of another study (VP-VYY-683-3101-PK01), there was no indication that age affected PK characteristics of iloperidone or its metabolites P88 and P95.</p>
	Sex	<p>Having adjusted for body size, exposure AUC for each of iloperidone, P88, and P95 is 48% larger in women than in men (VP-VYY-683-3101-PK01). The practical importance of this finding is uncertain, as there is no evidence that women have more tolerability or safety problems than men when receiving recommended doses of iloperidone (Integrated Summary of Safety).</p>
	Race	<p>No specific study was conducted to evaluate the effect of race or ethnic origin. In population PK analysis, no correlation was found between race (Caucasian, African-American, Asian, other) and plasma exposure (VP-VYY-683-3101-PK01).</p>
	Hepatic & Renal Impairment	<p>Hepatic Impairment (HI) (ILO522 0103)</p> <p>Iloperidone:</p> <ul style="list-style-type: none"> <li>- <math>C_{max}</math> (ng/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 1.75 (56)</li> <li>o HI: 1.68 (40)</li> <li>o % change: -4%</li> </ul> </li> <li>- <math>AUC_{0-\infty}</math> (ng*hr/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 22.0 (36)</li> <li>o HI: 26.2 (38)</li> <li>o % change: 19%</li> </ul> </li> </ul> <p>P88:</p> <ul style="list-style-type: none"> <li>- <math>C_{max}</math> (ng/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 1.02 (63)</li> <li>o HI: 1.74 (21)</li> <li>o % change: 71%</li> </ul> </li> <li>- <math>AUC_{0-\infty}</math> (ng*hr/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 32.3 (53)</li> <li>o HI: 47.8 (40)</li> <li>o % change: 48%</li> </ul> </li> </ul> <p>P95:</p> <ul style="list-style-type: none"> <li>- <math>C_{max}</math> (ng/mL) with (%CV)</li> </ul>

		<ul style="list-style-type: none"> <li>o Normal: 1.90 (32)</li> <li>o HI: 1.54 (70)</li> <li>o % change: -19%</li> </ul> <ul style="list-style-type: none"> <li>- AUC<sub>0-∞</sub> (ng*hr/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 71.5 (39)</li> <li>o HI: 68.1 (32)</li> <li>o % change: 5%</li> </ul> </li> </ul> <p><b>Renal Impairment (RI) (ILO522 0102)</b>  Iloperidone:</p> <ul style="list-style-type: none"> <li>- C<sub>max</sub> (ng/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 2.2 (35)</li> <li>o RI: 2.3 (71)</li> <li>o % change: 5%</li> </ul> </li> <li>- AUC<sub>0-∞</sub> (ng*hr/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 26.6 (23)</li> <li>o RI: 47.9 (82)</li> <li>o % change: 80%</li> </ul> </li> </ul> <p><b>P88:</b></p> <ul style="list-style-type: none"> <li>- C<sub>max</sub> (ng/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 2.01 (38)</li> <li>o RI: 2.00 (39)</li> <li>o % change: -0.5%</li> </ul> </li> <li>- AUC<sub>0-∞</sub> (ng*hr/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 62.5 (62)</li> <li>o RI: 44.9 (40)</li> <li>o % change: -28%</li> </ul> </li> </ul> <p><b>P95:</b></p> <ul style="list-style-type: none"> <li>- C<sub>max</sub> (ng/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 4.2 (58)</li> <li>o RI: 3.9 (54)</li> <li>o % change: -7%</li> </ul> </li> <li>- AUC<sub>0-∞</sub> (ng*hr/mL) with (%CV) <ul style="list-style-type: none"> <li>o Normal: 141.2 (48)</li> <li>o RI: 447.4 (61)</li> <li>o % change: 217%</li> </ul> </li> </ul>
Extrinsic Factors	Drug interactions	<p><b>Dextromethorphan (ILO522 0104)</b>  Iloperidone:</p> <ul style="list-style-type: none"> <li>- C<sub>max</sub> (ng/mL) with (%CV) <ul style="list-style-type: none"> <li>o ILO: 2.79 (27)</li> <li>o ILO+DEX: 2.75 (30)</li> <li>o % change: -1%</li> </ul> </li> <li>- AUC<sub>0-∞</sub> (ng*hr/mL) with (%CV) <ul style="list-style-type: none"> <li>o ILO: 29.4 (36)</li> <li>o ILO+DEX: 30.2 (40)</li> <li>o % change: 3%</li> </ul> </li> </ul>

		<ul style="list-style-type: none"> <li>o ILO+KETO: 160.4 (44)</li> <li>o % change: 38%</li> </ul> <p><b>Fluoxetine (ILO522 0108)</b></p> <p><b>Iloperidone:</b></p> <ul style="list-style-type: none"> <li>- <math>C_{max}</math> (ng/mL) with (%CV) <ul style="list-style-type: none"> <li>o ILO: 2.49 (31)</li> <li>o ILO+FLUOX: 4.22 (34)</li> <li>o % change: 41%</li> </ul> </li> <li>- <math>AUC_{0-\infty}</math> (ng*hr/mL) with (%CV) <ul style="list-style-type: none"> <li>o ILO: 27.1 (29)</li> <li>o ILO+FLUOX: 62.7 (23)</li> <li>o % change: 131%</li> </ul> </li> </ul> <p><b>P88:</b></p> <ul style="list-style-type: none"> <li>- <math>C_{max}</math> (ng/mL) with (%CV) <ul style="list-style-type: none"> <li>o ILO: 2.67 (27)</li> <li>o ILO+FLUOX: 4.39 (28)</li> <li>o % change: 64%</li> </ul> </li> <li>- <math>AUC_{0-\infty}</math> (ng*hr/mL) with (%CV) <ul style="list-style-type: none"> <li>o ILO: 54.2 (28)</li> <li>o ILO+FLUOX: 118.7 (28)</li> <li>o % change: 119%</li> </ul> </li> </ul> <p><b>P95:</b></p> <ul style="list-style-type: none"> <li>- <math>C_{max}</math> (ng/mL) with (%CV) <ul style="list-style-type: none"> <li>o ILO: 4.10 (42)</li> <li>o ILO+FLUOX: 1.21 (23)</li> <li>o % change: -70%</li> </ul> </li> <li>- <math>AUC_{0-\infty}</math> (ng*hr/mL) with (%CV) <ul style="list-style-type: none"> <li>o ILO: 127.1 (31)</li> <li>o ILO+FLUOX: 59.2 (29)</li> <li>o % change: -53%</li> </ul> </li> </ul>
	Food Effects	<p>No statistically significant differences were observed in the rate and extent of exposure (<math>C_{max}</math> and <math>AUC_{0-\infty}</math>) of iloperidone, P88, or P95 when iloperidone was administered as a tablet under fasted or fed conditions. (ILO522 0105)</p> <p><b>Iloperidone:</b></p> <ul style="list-style-type: none"> <li>- <math>C_{max}</math> (ng/mL) <ul style="list-style-type: none"> <li>o Fasted: <math>3.3 \pm 1.5</math></li> <li>o High Fat: <math>2.8 \pm 0.8</math></li> <li>o % change: -15%</li> </ul> </li> <li>- <math>AUC_{0-\infty}</math> (ng*hr/mL) <ul style="list-style-type: none"> <li>o Fasted: <math>44.4 \pm 19.7</math></li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>○ High Fat: 47.5 ± 19.1</li> <li>○ % change: 7%</li> </ul> <p>P88:</p> <ul style="list-style-type: none"> <li>- C<sub>max</sub> (ng/mL) <ul style="list-style-type: none"> <li>○ Fasted: 2.9 ± 0.8</li> <li>○ High Fat: 2.7 ± 0.8</li> <li>○ % change: -7%</li> </ul> </li> <li>- AUC<sub>0-∞</sub> (ng*hr/mL) <ul style="list-style-type: none"> <li>○ Fasted: 71.8 ± 24.4</li> <li>○ High Fat: 74.5 ± 21.2</li> <li>○ % change: 4%</li> </ul> </li> </ul> <p>P95:</p> <ul style="list-style-type: none"> <li>- C<sub>max</sub> (ng/mL) <ul style="list-style-type: none"> <li>○ Fasted: 3.6 ± 1.8</li> <li>○ High Fat: 2.9 ± 1.4</li> <li>○ % change: -19%</li> </ul> </li> <li>- AUC<sub>0-∞</sub> (ng*hr/mL) <ul style="list-style-type: none"> <li>○ Fasted: 130.9 ± 52.1</li> <li>○ High Fat: 121.7 ± 48.2</li> <li>○ % change: 7%</li> </ul> </li> </ul>
<p>Expected High Clinical Exposure Scenario</p>	<p>The maximum recommended human dose (MRHD) is 24 mg/day administered as 12 mg BID. In the thorough QT study (ILO522 2328), the average peak concentrations of iloperidone 24 mg QD in the absence and presence of the CYP2D6 inhibitor paroxetine (20 mg QD) and the CYP3A4 inhibitor ketoconazole (200 mg BID) was investigated.</p> <p>Iloperidone:</p> <ul style="list-style-type: none"> <li>- C<sub>max</sub> (ng/mL) with (%CV) <ul style="list-style-type: none"> <li>○ No inhibitors: 29.47 (39)</li> <li>○ With inhibitors: 46.56 (41)</li> <li>○ % change: 58%</li> </ul> </li> </ul> <p>P88:</p> <ul style="list-style-type: none"> <li>- C<sub>max</sub> (ng/mL) <ul style="list-style-type: none"> <li>○ No inhibitors: 33.12 (45)</li> <li>○ With inhibitors: 60.10 (50)</li> <li>○ % change: 81%</li> </ul> </li> </ul> <p>P95:</p> <ul style="list-style-type: none"> <li>- C<sub>max</sub> (ng/mL) <ul style="list-style-type: none"> <li>○ No inhibitors: 54.59 (50)</li> <li>○ With inhibitors: 14.44 (103)</li> <li>○ % change: -74%</li> </ul> </li> </ul>

## 6.2 TABLE OF STUDY ASSESSMENTS

**Table 3-7 Assessment schedule (Pre-treatment phase)**

Phase	Period	Pre-Treatment					
		Screen	Taper <sup>a</sup>	Wash-out and Baseline			
Evaluations	Day	-30 to -12	-11 to -5	-4 to -3	-2	-1	0
Informed consent		X					
Relevant medical history / Current medical condition(s)		X	X	X	X	X	X
Prior and current medications		X	X	X	X	X	X
Prior psychotropic medication(s)		X	X				
Screened Subject Log, Demography, DSM-IV diagnosis, Pharmacogenetics		X					
Meal Record					X	X	X
Inclusion/exclusion criteria		X		X			
Vital signs		X			Twice daily		
Electrocardiogram		X			XXX	XXX	XXXXXXXX
Laboratory evaluation		X <sup>a,c</sup>					X <sup>d</sup>
Physical examination		X					X <sup>e</sup>
IVRS call		X <sup>a</sup>			X <sup>a</sup>		
Urine drug screen		X					X <sup>d</sup>
Clinical Global Impression of Severity (CGI-S) score, Pregnancy test		X					X
Adverse events (serious events [SAEs] only)		X	X	X	X	X	X

<sup>a</sup> This Taper Period occurred in an outpatient setting. If deemed necessary by the Investigator, certain patients could undergo the Taper Period in an inpatient setting.

<sup>b</sup> Laboratory assessments could be repeated to confirm an abnormal finding for purposes of meeting inclusion/exclusion criteria.

<sup>c</sup> In addition to routine laboratory evaluations, hepatitis A and B and Thyroid Stimulating Hormone (TSH) tests were performed for screening purposes.

<sup>d</sup> Repeated at baseline only if the screening evaluations were performed more than 14 days before Day 0.

<sup>e</sup> IVRS was notified of the patient identification number at the screening visit. On Day -2, patients were randomized to treatment using IVRS. IVRS was also called to report patient completion or discontinuation.

**Table 3-8 Assessment schedule (Treatment phase)**

Phase	Period	Treatment phase												
		Treatment Period 1 <sup>a</sup>			Treatment Period 2 <sup>b</sup>			Treatment Period 3 <sup>c</sup> (Iloperidone treated patients only)						
Evaluations	Day	D1 to DY <sup>d</sup>	SSD1	SSD2	SSD3	DX <sup>e</sup> -DY <sup>d</sup>	SSD1	SSD2	SSD3	DX <sup>e</sup> -DY <sup>d</sup>	SSD1	SSD2	SSD3	SC <sup>f</sup>
Meal Record			X	X	X		X	X	X		X	X	X	
Vital signs		Twice daily												
Electrocardiogram		X <sup>g</sup>	XXX	XXX	XXXXXXXX	X <sup>g</sup>	XXX	XXX	XXX	X <sup>g</sup>	XXX	XXX	XXX	X
Laboratory evaluation, Physical exam, CGI-S														X
IVRS call														X <sup>h</sup>
Pharmacokinetic (PK) sample			X <sup>i</sup>	X <sup>i</sup>			X <sup>i</sup>	X <sup>i</sup>			X <sup>i</sup>	X <sup>i</sup>		X
Pregnancy test, urine drug screen														X
Concomitant medications	Daily	X	X	X		X	X	X	X	X	X	X	X	X
Drug administration record (DAR)	Daily	X	X	X		X	X	X	X	X	X	X	X	X <sup>k</sup>
Adverse events (AEs), serious AEs (SAEs)	Daily	X	X	X		X	X	X	X	X	X	X	X	X
Study Completion (SC) form														X

<sup>a</sup> SSD1, 2, and 3 were the following study days for: ILO LOW=13,14,15; ILO HIGH=15, 16, 17; ILO QD=16, 17, 18; RIS=11, 12, 13; ZIP=8, 9, 10; QUET=10, 11, 12.

<sup>b</sup> Patients received one metabolic inhibitor in addition to the assigned treatment during this period: Iloperidone- and (prior to Amendment 2; see Section 4.1) risperidone-treated patients received paroxetine 20 mg q.d., and ziprasidone- and quetiapine-treated patients received ketocoazole 200 mg b.i.d. Note: Based on Amendment 2 (see Section 4.1.), the PM dose of ketoconazole was not given on the last day of study drug administration. SSD1, 2, and 3 are the following study days for: ILO LOW=21, 22, 23; ILO HIGH=23, 24, 25; ILO QD=24, 25, 26; RIS=19, 20, 21; ZIP=13, 14, 15; QUET=15, 16, 17.

<sup>c</sup> In addition to paroxetine, patients randomized to Iloperidone received ketoconazole 200 mg b.i.d. during this period. Patients randomized to any other treatment did NOT enter this period. During this period, SSD1, 2, and 3 were the following study days for: ILO LOW=26, 27, 28; ILO HIGH=28; 29, 30; ILO QD = 29, 30, 31.

<sup>d</sup> Day Y (DY) is the day immediately prior to SSD1 of this period. The corresponding study day is dependent on treatment assignment (see Tables 3-3 and 3-4).

<sup>e</sup> Day X (DX) is the day immediately following SSD3 of the prior period. The corresponding study day is dependent on treatment assignment (see Tables 3-3 and 3-4).

<sup>f</sup> SC=study completion evaluation conducted the morning following SSD3 of Period 2 or 3, depending on treatment assignment, or at premature discontinuation. Quetiapine, ziprasidone, and risperidone-treated patients had study completion evaluations performed the morning following SSD3 of Period 2. Iloperidone-treated patients had study completion performed the morning following SSD3 of period 3.

<sup>g</sup> One ECG was performed on the second day of each period (ILO HIGH=Days 2, 19, and 27; ILO LOW=Days 2, 17, 25; ILO QD=Days 2, 20, 28; and RIS=Days 2, 15; ZIP=Days 2, 12; QUET=Days 2, 14)

<sup>h</sup> The IVRS was called to report patient completion or discontinuation.

<sup>i</sup> 3 blood samples drawn from patients in the ILO group, 2 from patients in the ZIP, QUET, and (prior to Amendment 2; see Section 4.1) RIS groups.

<sup>j</sup> Three blood samples for pharmacokinetic analysis were drawn from patients in the Iloperidone group.

<sup>k</sup> Performed only at premature discontinuation.

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/s/

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