NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Clinical Development

Compound/Project: Iloperidone/CILO522A

Study No: ILO522 2328

A randomized, open-label, multicenter, 5-arm, safety study 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

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I certify that this report accurately describes the conduct and the results of this clinical study.

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A list of all investigators and centers can be found in Appendix 2.2.

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List of abbreviations

α1,2	alpha adrenergic receptor, subtypes 1 and 2
5HT2, 2A, 6	5-hydroxytryptamine (serotonin) receptor, subtypes 2, 2A, and 6
AE	Adverse event
ALT	Alanine aminotransferase, SGPT, glutamic pyruvic transaminase
a.m.	*ante meridian* (Latin: before noon)
AST	Aspartate aminotransferase, SGOT, glutamic oxaloacetic transaminase
β-hCG	Human chorionic gonadotropin (beta subunit)
b.i.d.	*bis in die* (Latin: twice a day)
BMI	body mass index
BP	blood pressure
b.p.m.	beats per minute
BUN	Blood urea nitrogen
CGI-S	Severity of Illness scale of the Clinical Global Impression
CPK	Creatine phosphokinase
CR	Clinical Research
CRO	Contract Research Organization
CS&E	Clinical Safety and Epidemiology
CTL	Clinical Trial/Study Leader
DAR	Drug Administration Record
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DNDP	Division of Neuropharmacological Drug Products
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
FDA	Food and Drug Administration
HbcAb	Hepatitis B core antibody
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ILO	Iloperidone
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
NDC	National Drug Code
NYHA	New York Heart Association

PD	Pharmacodynamics
PK	Pharmacokinetics
p.m.	*post meridian* (Latin: after noon)
p.o.	*per os* (Latin: by mouth, orally)
p.r.n.	*pro re nata* (Latin: as needed)
q.d.	*Quaque die* (Latin: every day)
QT	the QT interval of the ECG waveform
QTc	Corrected QT value
QTcF, QTcB	Fridericia and Bazett corrections of QT duration
QUET	Quetiapine
REB	Research Ethics Board
RIS	Risperidone
SAE	Serious adverse event
SC	Study completion
SGOT	Serum glutamic-oxaloacetic transaminase (also AST, aspartate aminotransferase)
SGPT	Serum glutamic-pyruvic transaminase (also ALT, alanine aminotransferase)
SOP	Standard operating procedure
SSD 1, 2 and 3	Steady-State Day(s) 1, 2 and 3
T_{max}	The time at which maximum blood concentrations are reached
ULN	Upper limit of normal range
US	United States
WHO	World Health Organization
ZIP	Ziprasidone

Study synopsis

Name of finished product: To be determined **Name of active ingredient:** Iloperidone

Title of study: A randomized, open-label, multicenter, 5-arm, safety study 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

Investigators: Dr. Mohammad Alam, Dr. Jeffrey Borenstein, Dr. David Brown, Dr. John Carman, Dr. Ram Gopalan, Dr. Michael Lesem, Dr. Rick Mofsen, Dr. Steven Potkin, Dr. Sheldon Preskorn, Dr. Thomas Shiovitz, Dr. Tram Tran-Johnson, Dr. Craig Wronski

Study center(s): 12 centers in the US enrolled patients

Publication(s): No publications have been written/are planned at this time.

Study period: First patient enrolled: 27-Nov-01 Last patient completed: 03-May-02

Development phase: IIa

Objectives: The primary objective of this study was to characterize the effect of iloperidone (at 8 mg b.i.d. and 12 mg b.i.d.) on the duration of the QTc interval in 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).

Methodology:

A central facility was used in this study for interpretation and analysis of ECGs. ECG tracings were produced and transmitted via modem to the central ECG facility for interpretation by a blinded reader.

This study had 2 phases:

1) Pre-treatment Phase, consisting of a Screening Period (Day -30 to –12), a Taper Period (Day -12 to –5), and a Washout/Baseline Period (Day -4 to 0). Patients were randomized in a ratio of 1:1:1:1:1 to receive iloperidone 8 mg b.i.d., iloperidone 12 mg b.i.d, iloperidone 24 mg q.d., ziprasidone 80 mg b.i.d., or quetiapine 375 mg b.i.d. Randomization was stratified based on gender in order to assure equal distribution of males and females in each treatment arm. Baseline ECGs were conducted over 3 days (Day -2, 1, 0).

2) Treatment Phase, consisting of 3 treatment periods: Treatment Period 1 (dose titration and steady state without metabolic inhibition), Treatment Period 2 (addition of 1 metabolic inhibitor), and Treatment Period 3 (addition of a second metabolic inhibitor to the iloperidone groups). During Treatment Period 1, patients followed fixed dosing regimens to achieve the target dosage of their

assigned study medication (ziprasidone by Day 6; iloperidone 8 mg b.i.d. and quetiapine by Day 8; iloperidone 12 mg b.i.d. by Day 10; iloperidone 24 mg q.d. by Day 11). ECGs were recorded on three successive days after steady-state levels were attained. During Treatment Period 2, an inhibitor of the primary cytochrome P450 isoenzyme was added to each arm. (For ziprasidone and quetiapine, ketoconazole was added for 2 days before ECG assessments were conducted; for the iloperidone groups, paroxetine was added to regimen for 5 days before ECG assessments were conducted). During Treatment Period 3, only iloperidone patients received ketoconazole in addition to paroxetine for 2 days before ECG assessments were conducted.

Number of patients: One hundred eighty-eight patients were randomized to study medication. Eight patients discontinued before receiving the first dose of study medication; therefore, 180 patients were randomized and received study medication. Of these patients, 34 patients were randomized to iloperidone 8 mg b.i.d., 35 to iloperidone 12 mg b.i.d., 37 to iloperidone 24 mg q.d., 34 to ziprasidone 80 mg b.i.d., 35 to quetiapine 375 mg b.i.d., and 5 to risperidone 4 mg b.i.d. (risperidone arm was removed following Amendment 2, dated 9-Jan-02).

Indication and main criteria for inclusion: Male and female patients 18 to 65 years of age with schizophrenia or schizoaffective disorder (diagnosis according to the DSM-IV criteria) without a history or clinical evidence of clinically significant cardiovascular disease.

Investigational drug: Iloperidone was formulated as tablets containing either 1, 2, 4, 6, 8, or 10 mg of iloperidone. Batch and formulation numbers were as follows:

Product	Batch No.	Formulation No.
Iloperidone 1 mg tablets	F0450799	3752748.00.006
Iloperidone 2 mg tablets	F0261001	3752870.00.004
Iloperidone 4 mg tablets	F0480799	3752862.00.006
Iloperidone 6 mg tablets	F0291001	3752755.00.008
Iloperidone 8 mg tablets	F0140400	3752854.00.007
Iloperidone 10 mg tablets	F0150400	3758349.00.002

Reference therapy: Risperidone (supplied as Risperdal®) was formulated as a tablet containing either 1, 2, 3, or 4 mg of risperidone (following Amendment 2, the risperidone treatment arm was removed); quetiapine (supplied as Seroquel®) was formulated as a tablet containing either 25, 100, 200 or 300 mg of quetiapine; ziprasidone (supplied as Geodon®) was formulated as a capsule containing 20, 40, 60, or 80 mg of ziprasidone. Batch numbers and National Drug Code (NDC) numbers for the reference therapies were as follows:

Product	Batch No.	NDC No.
Risperidone 1 mg tablets	91P0743E	50458-0300-06
Risperidone 2 mg tablets	91P0850	50458-0320-06
Risperidone 3 mg tablets	91P0968E	50458-0330-06
Risperidone 4 mg tablets	91P1019	50458-0350-06
Quetiapine 25 mg tablets	3080H, 3675F	00310-0275-10
Quetiapine 100 mg tablets	3704F, 4690F	00310-0271-10
Quetiapine 200 mg tablets	3737F, 4508F	00310-0272-10
Quetiapine 300 mg tablets	3193H, 4523C	00310-0274-60
Ziprasidone 20 mg capsules	0326K01E, 0578K01D	0049-3960-60
Ziprasidone 40 mg capsules	0401K01D	0049-3970-60
Ziprasidone 60 mg capsules	0414K01E	0049-3980-60
Ziprasidone 80 mg capsules	0891K00D, 1132K01A	0049-3990-60

Note: Following Amendment 2, the risperidone treatment arm was removed.

Metabolic inhibitors: an inhibitor of the specific cytochrome P450 isoenzyme responsible for the metabolism of the study drugs was added to each arm; paroxetine was supplied as Paxil® and ketoconazole was supplied as Nizoral®. Batch numbers and NDC numbers were as follows.

Product	Batch No.	NDC No.
Paroxetine 20 mg tablets	20551B11, 4540B11	00029-3211-20
Ketoconazole 200 mg tablets	91P0982E, 91P1006	50458-0220-10

Duration of treatment: Total treatment duration was 28, 30, 31, 15, 17, and 21 days for patients randomized to iloperidone 8 mg b.i.d., iloperidone 12 mg b.i.d., iloperidone 24 mg q.d., ziprasidone 80 mg b.i.d, quetiapine 375 mg b.i.d., and risperidone 4 mg b.i.d., respectively. (Following Amendment 2, the risperidone treatment arm was removed.)

Criteria for evaluation:

Efficacy: Efficacy was not evaluated in this study. However, the Severity of Illness scale of the Clinical Global Impression (CGI-S) was used to monitor the clinical status of the patients during the study.

Safety: The effects of study medication on the QTc interval of the electrocardiogram were assessed using the following parameters: the mean change from baseline in QTc, incidence of increases from baseline of QTc ≥30 msec, ≥60 msec, and incidence of QTc of ≥500 msec. Other safety and tolerability measures were adverse events (AEs), clinical laboratory evaluations (including hematology, biochemistry, and urinalysis), vital signs, physical examinations, and pregnancy tests.

Pharmacology: Blood samples for measurement of treatment drug plasma levels were collected at the estimated time of maximum and trough concentration for each compound on Steady State Day 1 and Steady State Day 2 of each Treatment Period. An additional sample was collected at 4 hours post-dose for iloperidone-treated patients, which coincides with the time of maximum concentration of the primary active metabolite, P88.

Additional Evaluations: Collection of pharmacogenetic samples was performed optionally. Neither genotypes nor phenotypes were pre-specified for this investigation. Hence, all statistical analyses performed are considered exploratory. Results from these analysis will be summarized in a separate report.

Statistical methods: All four correction factors (Bazett, Fridericia, the FDA 0.37 exponent, and baseline corrected) were used for calculating QTc intervals. The Fridericia method was defined as the primary correction method. The primary variable of interest was the QTc change from baseline to steady state at T_{MAX} of treatment period 1. For each treatment group, ninety-five percent confidence intervals were constructed for the mean QTc change from baseline around T_{MAX}.

Results: A total of 188 patients were randomized to the study; of these, 149 patients completed the study (79%). The completion rate was similar across treatment arms, with the most common reason for discontinuation being withdrawal of consent. Five patients were randomized to risperidone before this treatment arm was removed following amendment 2, dated 9-Jan-02.

Demographic information, background characteristics, past medical conditions, prior medication and therapies, and severity of illness were similar among the 5 treatment arms.

Primary QTc Analysis: The primary QTc analysis was the analysis of the primary variable (QTc change at T_{MAX} from baseline to steady state of treatment period 1) on the primary QTc population [included all patients who had at least 50% (≥5) of the QTc evaluations on days SSD1, SSD2, and SSD3 at T_{MAX} during Treatment Period 1 and at least half (≥5) of the QTc evaluations around times that corresponded to the T_{MAX} for each compound at baseline (Days –2, -1 and 0)].

Mean QTcF change was similar for iloperidone 8 mg b.i.d. (8.5±10.5 msec), iloperidone 12 mg b.i.d. (9.0±12.5 msec), and ziprasidone 80 mg b.i.d. (9.6±11.0 msec). Quetiapine 375 mg b.i.d. (1.3±11.1 msec) was associated with the smallest mean change from baseline at T_{max} in QTcF and iloperidone 24 mg q.d. (15.4±11.7 msec) was associated with the largest mean change from baseline at T_{max} in QTcF.

Secondary QTc Analysis: The secondary QTc analysis was the analysis of primary and secondary variables on the primary and secondary QTc population [all patients who had at least one QTc evaluation at baseline (Days –2, -1, 0) and at least one ECG post-baseline at steady state with or without metabolic inhibitors present]. The results of the secondary analysis are summarized by Treatment Period:

For Treatment Period 1, the results for mean change in QTcF from baseline at T_{max} did not differ substantially from results obtained using the primary population. The number of patients (%) with QTcF increases of $\geq$ 30 msec from baseline to steady state during Treatment Period 1 was greatest in the iloperidone 24 mg q.d. [19 (61%)] group followed by the ziprasidone 80 mg b.i.d. [17 (52%], iloperidone 12 mg b.i.d. [15 (44%)], iloperidone 8 mg b.i.d. [9 (31%)] and quetiapine [4 (12%)] groups, respectively. Two patients in Treatment Period 1 experienced increases in QTcF of $\geq$ 60 msec from baseline to steady state at T_{max}. One patient was in the iloperidone 8 mg b.i.d. group and the other was in the iloperidone 24 mg q.d. group.

During Treatment Period 2 (the presence of one metabolic inhibitor), the mean change in QTcF from baseline to steady state at T_{max} was highest in the iloperidone 24 mg q.d. (17.5$\pm$10.3) and ziprasidone 80 mg b.i.d. (15.9$\pm$11.8) groups, followed by the iloperidone 12 mg b.i.d. (11.6$\pm$16.8) and iloperidone 8 mg b.i.d. (11.2$\pm$12.0) groups. The smallest mean change from baseline to steady state at T_{max} during Treatment Period 2 was observed in the quetiapine 375 mg b.i.d. (2.6$\pm$11.5) group. In comparison to Treatment Period 1, the mean change QTcF at T_{max} was numerically higher in all treatment groups. The percentage increase from Treatment Period 1 to Treatment Period 2 in QTcF at T_{max} was greatest in the ziprasidone (60%) and quetiapine (50%) arms followed by the iloperidone 12 mg b.i.d. (29%) and iloperidone 8 mg b.i.d. (26%) treatment arms. The smallest percentage increase in QTcF at T_{max} from Treatment Period 1 to Treatment Period 2 was observed in the iloperidone 24 mg q.d. group (14%).

The number of patients (%) with QTcF increases of $\geq$ 30 msec from baseline to steady state at T_{max} during Treatment Period 2 was greatest in the iloperidone 24 mg q.d. [22 (71%)] group, followed by the ziprasidone 80 mg b.i.d. [18 (60%], iloperidone 8 mg b.i.d. [14 (54%)], iloperidone 12 mg b.i.d. [15 (48%)], and quetiapine [6 (19%)] groups, respectively. In Treatment Period 2, the proportion of patients with QTcF increases at of $\geq$ 30 msec at Tmax in the iloperidone 12 mg b.i.d., iloperidone 24 mg q.d., and ziprasidone 80 mg b.i.d. was similar to Treatment Period 1. The proportion of patients with QTcF increases of $\geq$ 30 msec from baseline to steady state at Tmax in the iloperidone 8 mg b.i.d. and quetiapine 375 mg b.i.d. groups was higher in Treatment Period 2 compared with Treatment Period 1.

Two patients in Treatment Period 2 experienced increases in QTcF of $\geq$ 60 msec from baseline to steady state at T_{max}. One patient was in the iloperidone 8 mg b.i.d. group and the other was in the iloperidone 24 mg q.d. group.

During Treatment Period 3, in which a second metabolic inhibitor was added to the regimen of iloperidone-treated patients, the mean change in QTcF from baseline to steady state at T_{max} was highest in the iloperidone 24 mg q.d. (19.5$\pm$11.9) and iloperidone 12 mg b.i.d. (19.3$\pm$17.1) groups, followed by the iloperidone 8 mg b.i.d. (15.7$\pm$14.1) group. The percentage increase in QTcF at T_{max} from Treatment Period 2 to Treatment Period 3 was greatest in the iloperidone 12 mg b.i.d. group (66%), followed by the iloperidone 8 mg b.i.d. (40%), and the iloperidone 24 mg q.d. (11%) groups, respectively.

The number of patients (%) with QTcF increases of $\geq$ 30 msec from baseline to steady state at T_{max} during Treatment Period 3 was greatest in the iloperidone 24 mg q.d. [21 (70%)] and iloperidone 12 mg b.i.d. [20 (69%)] groups followed by the iloperidone 8 mg b.i.d. [13 (52%)] group.

In Treatment Period 3, the proportion of patients with QTcF increases of $\geq$ 30 msec at T_{max} in the iloperidone 8 mg b.i.d. and 24 mg q.d. treamtent groups was similar to that observed in Treatment Period 2. The proportion of patients with QTcF increases of $\geq$ 30 msec at T_{max} in the iloperidone 12 mg b.i.d. was greater in Treatment Period 3 than in Treatment Period 2.

Four patients in Treatment Period 3 experienced increases in QTcF of ≥ 60 msec from baseline to steady state at T_{max}. One patient was in the iloperidone 8 mg b.i.d. group and the other 3 patients were in the iloperidone 12 mg b.i.d. group.

No patients experienced QTc values (using any correction factor) of ≥ 500 msec during this study.

Safety: The safety analysis included all patients who received at least one dose of study medication and from whom at least one safety measurement was obtained post-baseline. A total of 180 patients were included in the analysis (including 5 patients who were randomized to risperidone).

No deaths were reported. Three SAEs occurred during the study while patients were receiving study medication. One patient randomized to iloperidone 8 mg b.i.d. experienced tachycardia, one patient randomized to iloperidone 24 mg q.d. experienced inadequate control of diabetes mellitus, and one patient randomized to quetiapine 375 mg b.i.d. experienced aggravation of psychosis. Additionally, one SAE occurred before randomization to study medication and one SAE occurred after study medication was discontinued.

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. The most common treatment-emergent AEs (≥10%) reported for patients in the ziprasidone group included headache, EPS, dyspepsia, fatigue, nausea, anxiety, insomnia, somnolence, akathisia, constipation, and sedation. The most common treatment-emergent AEs (≥10%) reported for patients for patients in the quetiapine group included sedation, dry mouth, somnolence, dizziness, constipation, dyspepsia, and fatigue.

The incidence of AEs that resulting in discontinuation was under 10% [definitely not similar] across treatment groups (iloperidone 8 mg b.i.d.=9%, iloperidone 12 mg b.i.d.=5%, iloperidone 24 mg q.d.=3%, ziprasidone=6%, quetiapine=3%).

Analyses of laboratory values showed little differences across treatment groups. In general, no dose-dependent effects on changes in laboratory values from baseline were observed among the iloperidone groups.

As seen in previous iloperidone studies, mean heart rate increased by approximately 10 b.p.m. for all iloperidone treatment groups during the first week and returned to near baseline values by week 3. Mean systolic blood pressure did not change substantially in any iloperidone treatment group over the course of this study. Mean diastolic blood pressure decreased gradually by ≈5mmHg in all iloperidone treatment groups over the course of the study.

During treatment period 1, the number of patients experiencing clinically notable increases in pulse rates was highest in the iloperidone 8 mg b.i.d. (24%) and iloperidone 24 mg q.d. (23%), similar in the iloperidone 12 mg b.i.d. (11%) and quetiapine (14%) groups, and lowest in the ziprasidone group (3%). The number of patients experiencing clinically notable increases in pulse rates during treatment period 2 decreased in all iloperidone treatment groups and continued to decrease in period 3. The number of clinically notable increases in pulse rates remained constant in treatment period 2 for both ziprasidone and quetiapine groups.

The incidence of clinically notable decreases in systolic blood pressure was greatest in the iloperidone 8 mg b.i.d. in all three treatment periods (ILO 8 mg b.i.d.= 18%, 11%, and 8%, respectively; ILO 12 mg b.i.d. = 3%, 3%, and 3%, respectively; ILO 24 mg q.d. = 9%, 0%, and 3%, respectively; quetiapine = 6% and 3%, respectively; ziprasidone 0% and 0%). The incidence of clinically notable decreases in diastolic pulse was similar in all treatment groups.

ECG abnormalities which were newly occurring or worsened from baseline (baseline included all ECG recorded on Days –2, -1, and 0) were observed in 35%, 32%, and 46% of the iloperidone-treated patients in the 8 mg b.i.d., 12 mg b.i.d., and 24 mg q.d. groups, respectively, and in 41% of ziprasidone and 40% of quetiapine-treated patients. No substantial differences were observed between treatment groups in individual newly occurring or worsening abnormalities. None of these ECG findings were associated with cardiovascular AEs.

The incidence of clinically notable increases in weight was higher in the iloperidone 8 mg b.i.d. (13%) and iloperidone 24 mg q.d. (16%) groups than the iloperidone 12 mg b.i.d. The mean change in weight from baseline to endpoint was similar in the iloperidone 8 mg b.i.d. (3.2 kg) and iloperidone 24 mg q.d. (3.3 kg). The mean change in weight from baseline to endpoint was lower in the iloperidone 12 mg b.i.d. (1.2 kg).

Pharmacology: Iloperidone mean peak steady-state concentrations in the absence of metabolic inhibition (Treatment period 1) were 12.35 ng/mL, 20.88 ng/mL, and 29.47 ng/mL for iloperidone 8 mg bid, 12 mg bid, and 24 mg qd respectively. These concentrations increased 29-64% in the presence of paroxetine (Treatment period 2), and 54-134% in the presence paroxetine and ketoconazole (Treatment period 3). The corresponding increases for P88 concentrations were similar. For P95, the concentrations reduced to ~50% and ~30% in the presence paroxetine and in the presence of paroxetine + ketoconazole, respectively. Within treatment periods, QTc changes tended to increase with concentrations of iloperidone (at Treatment period 2, $p<0.01$) and its metabolite P88 (at Treatment periods 2 and 3, $p< 0.02$).

Conclusions: This study provides evidence that administration of iloperidone at 16-24 mg/day is associated with a prolongation of the QT interval. Mean change from baseline in QTcF at T_{max} was similar to ziprasidone 80 mg b.i.d. when iloperidone was administered at doses of 8-12 mg b.i.d. Administration of iloperidone 24 mg q.d. produced a greater effect on QTcF. Metabolic inhibition increased the effect of iloperidone on the QTcF duration, especially when both the CYP3A4 and CYP2D6 pathways were inhibited. In the presence of both ketoconazole and paroxetine, the difference in mean change from baseline in QTcF at T_{max} between the twice daily and once daily iloperidone regimens was minimal.

Administration of iloperidone 16-24 mg/day given as either a b.i.d. or q.d. regimen did not cause a substantial number of patients to experience QTc values or changes in QTc values that were of clear clinical concern.

Date of the report: 09-Aug-02

Ethics and Good Clinical Practice

This study was performed in accordance with standard operating procedures of the sponsor (Novartis), operating at the time of the study. These were designed to ensure adherence to GCP and ensure the protection of the patients, as required by the following directives in operation at the time:

1. Declaration of Helsinki, concerning medical research in humans ('Recommendations Guiding Physicians in Biomedical Research Involving Human Patients', Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, 1996).
2. Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning Informed Patient Consent and IRB approval.

1 Introduction

Iloperidone is a benzisoxazole-piperidinyl derivative and is currently under development as a treatment for symptoms of schizophrenia. Iloperidone exerts selective blockade at several monoamine receptors, including dopaminergic D2, serotoninergic 5-HT2A, and adrenergic 1 and 2C receptors (Kalkmann et al 2001). While iloperidone has some characteristics similar to previously developed atypical antipsychotics, such as a high 5-HT2A / D2 binding ratio, the profile of this molecule is also distinct from other molecules in this class. For example, it has low affinity for histamine receptors, which may reduce the risk of weight gain and sedation seen with olanzapine and clozapine; and has high affinity for 2C-adrenergic receptors and 5-HT6, which may confer unique therapeutic properties.

The clinical development program to date has included seven phase II studies [(ILPB200, 201, 202, 203, 205, 303, and ILP2001)] and seven phase III studies. The phase III studies include three placebo-controlled efficacy studies [(ILP3000, 3004, and 3005)], three long-term safety studies [(ILP3001, 3002, and 3003)] and one study conducted in elderly patients [(ILP3007)]. The placebo-controlled studies evaluated a range of iloperidone doses (from 4 to 24 mg/d) administered b.i.d. over a period of 6 weeks. These studies demonstrated clinical improvement with iloperidone on a variety of efficacy rating scales. The effects of iloperidone appeared to be dose-dependent, with higher doses associated with a greater probability of therapeutic effect. Adverse events reported during treatment with iloperidone were consistent with the pharmacological properties of the drug, including a mild increase in heart rate and reduction in blood pressure and reports of mild dizziness. These events were generally well tolerated and rarely caused premature discontinuation from studies. Iloperidone was associated with modest weight gain, did not increase serum prolactin levels and produced a lower incidence of few extrapyramidal symptoms when compared to risperidone and haloperidol. The results from the clinical development program to date support the efficacy and safety of iloperidone in controlling psychotic symptoms associated with schizophrenia.

An emerging area of focus in the evaluation of drug safety is the effect of non-cardiac medications on the QT interval of the electrocardiogram (ECG). The duration of the QT interval is a measure of the repolarization period for the cardiac muscle following ventricular depolarization. It is thought that the primary mechanism of action by which non-cardiac medication prolong the duration of the QT interval is through inhibition of the Human Ether-a-go-go Related Gene (HERG) channel, a potassium channel directly involved in ventricular repolarization. The clinical significance of the magnitude of effect on QTc (corrected QT) duration observed with these compounds continues to be debated. However, this effect and its relationship to torsades de pointes (TdP) arrhythmia (Moss 1999) has received increased attention from regulatory authorities, resulting in labeling warnings, and even the withdrawal of several medications from the market. Certain risk factors such as female gender, advanced age, bradycardia, cardiovascular disease, and electrolyte abnormalities may increase the risk of torsades (Cavero et al 2000). Further, the risk of torsades may also be increased for certain medications that have the propensity to increase QTc when given concomitantly with agents that inhibit their metabolism through the cytochrome P450 enzyme system (Ilari, P, 2002; Webster, R, 2001).

Antipsychotics, both typical and atypical, have been associated with an increase in the duration of the QTc interval [Glassman. AJP Nov. 2001]. A recent study comparing the effect of several marketed antipsychotics on QTc duration showed thioridazine to be associated with the highest degree of QTc prolongation, followed by ziprasidone. Quetiapine, risperidone, olanzapine, and haloperidol were also associated with a prolongation of the QTc interval, but to a lesser extent (Zeldox briefing document 2000). In this study of marketed antipsychotics, minimum increase in QTc was observed when metabolic inhibitors of the CYPP450 isoenzyme responsible for metabolism of these drugs were added (with the exception of haloperidol – in which a doubling of QTc change was seen).

As has been seen with other antipsychotics, iloperidone has been observed to have some effects on QTc duration, although the magnitude of this effect has not fully been determined. Two preclinical safety studies were conducted in which the potential for effects of iloperidone and its metabolites on QTc prolongation were assessed. In the first study, iloperidone and its primary active metabolite, P88, showed high affinity for HERG (Ikr) channel, whereas, the other major metabolite (inactive) of iloperidone, P95, had a very low affinity for this channel (Novartis, data on file). The second conducted in vitro in dog Purkinje fibers showed iloperidone and P88, but not P95, to have a significant effect on action potential duration (APD) (Novartis, data on file). In clinical studies conducted thus far, iloperidone has been observed to have inconsistent effects on QTc interval duration (0.1-8.5 msec increase in QTc [Fridericia] from baseline to endpoint). However, these clinical studies were not primarily designed to assess changes in the duration of the QTc interval.

The current study was conducted to evaluate the effect of iloperidone on the QTc interval of the ECG under controlled conditions.

2 Study objectives

The objectives of this study were:

Primary

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.

Secondary

To evaluate the effect of iloperidone on QTc interval duration when given as a 24 mg once-daily dosing regimen.

To evaluate the effect of iloperidone in the presence of metabolic inhibitors (paroxetine and ketoconazole) on QTc interval duration.

To evaluate the plasma concentration-effect relationship of iloperidone, and of its primary metabolite, P88, on QTc interval duration.

To descriptively compare the effect of iloperidone to the effects of the antipsychotics ziprasidone, quetiapine and risperidone on the QTc interval. (Following protocol

Amendment 2, dated 09-Jan-2002, risperidone was removed from this comparison; see Section 4.1 for details).

3 Investigational plan

3.1 Overall study design

This was a prospective, randomized, open-label, 5-arm (Amendment 2; see Section 4.1) study measuring the effect of iloperidone on QTc duration relative to baseline. It was planned that 35 patients per treatment arm would be randomized (assignment ratio 1:1:1:1:1). All patients underwent 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 treated with iloperidone underwent one additional period, Treatment Period 3, in which a second metabolic inhibitor was added (i.e., iloperidone-treated patients were given paroxetine in Treatment Period 2, and then received ketoconazole in addition to paroxetine in Treatment Period 3). During the Screening and Taper Periods, patients were assessed as outpatients; thereafter, all patients were assessed on an in-patient basis (if deemed necessary by the Investigator, certain patients underwent the Taper Period as inpatients).

3.1.1 Pre-treatment phase

The pre-treatment phase consisted of three periods: Screening, Taper, and Washout/Baseline. This phase encompassed Days -30 to 0 (Table 3-1).

Table 3-1 Study Design (Pre-treatment phase)

Phase	Pre-treatment phase		
Period	Screening	Taper	Washout and Baseline[a]
Study Day	-30 to –12	-11 to -5	-4 to 0
Drug	Prior antipsychotic	Prior antipsychotic	-

[a] Baseline ECG assessments were conducted on Days -2, -1, and 0. Day 0 was considered baseline for all other assessments.

Screening Period

The screening visit occurred between Day -30 and Day -12.

Taper Period

Prior antipsychotic medications were tapered off over approximately 7 days (Days -11 to -5), as needed. This taper occurred in an outpatient setting. If deemed necessary by the Investigator, certain patients underwent the Taper Period in an inpatient setting.

Washout and Baseline Period

During Days -4 to 0, patients were hospitalized and free of antipsychotic medications. Baseline ECG assessments were conducted on Days -2, -1, and 0. Day 0 was considered baseline for all other assessments.

3.1.2 Treatment phase

The treatment phase consisted of 3 periods: Treatment Periods 1, 2, and 3 (Table 3-2).

Table 3-2 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.

Treatment Period 1

During Treatment Period 1, patients followed fixed dosing regimens to achieve the target dosage of their assigned study medication (ziprasidone by Day 6; iloperidone 8 mg b.i.d. and quetiapine by Day 8; iloperidone 12 mg b.i.d. by Day 10; iloperidone 24 mg q.d. by Day 11).

Patients treated with iloperidone or (prior to Amendment 2; see Section 4.1) risperidone received the target dose for 5 days before steady-state ECG assessments were conducted. Patients treated with ziprasidone or quetiapine received the target dose for 2 days before steady-state ECG assessments were conducted. ECG assessments were performed for 3 days after reaching steady state.

Treatment Period 2

During this period, an inhibitor of the specific cytochrome P450 isoenzyme that is primarily responsible for metabolism of each study drug was added to the treatment regimen of patients in each treatment arm. For ziprasidone- and quetiapine-treated patients, ketoconazole 200 mg b.i.d., an inhibitor of CYP3A4, was added to the respective treatment regimen for 2 days before steady-state ECG assessments were conducted. Patients treated with risperidone (prior to Amendment 2; see Section 4.1) or iloperidone had paroxetine, an inhibitor of CYP2D6, added to the respective regimen for 5 days before steady-state ECG assessments were conducted.

Treatment Period 3

Only patients who were randomized to iloperidone underwent this period. In addition to paroxetine, iloperidone-treated patients received ketoconazole for 2 days before ECG assessments were conducted over 3 additional days.

3.2 Discussion of design

Previous clinical studies with iloperidone were not designed specifically to assess changes in the duration of the QTc interval. In all of these studies, changes in QTc were based on one baseline and one endpoint evaluation. Due to the inherent variability in QT duration, changes induced by a medication are difficult to ascertain without a comprehensive measurement of the patient's baseline values (Morganroth et al 1991, Molnar et al 1996). Therefore, this study was designed to evaluate the effects of iloperidone on QTc duration under controlled conditions using comprehensive ECG measurements at baseline and post-baseline assessments.

Doses of iloperidone

Data from placebo-controlled Phase III studies of iloperidone showed QTcF (Fridericia correction) increases of 0.1 to 8.5 msec at doses of 4-24 mg/d when comparing a single ECG at baseline to a single ECG at endpoint. At lower doses of iloperidone (4 mg–16 mg) QTc prolongation was minimal (0.1–5 msec). In the most recently completed iloperidone study, [ILP3005], a greater prolongation (~8.5 msec) was observed when higher doses of iloperidone (20-24 mg/d) were studied. The current study, CILO522A2328, included doses of 8 mg b.i.d. and 12 mg b.i.d. in order to evaluate the effect of iloperidone on QTc at these higher doses. This study also evaluated the safety of 24 mg/d given q.d., as it was unknown whether higher peak concentrations and/or greater fluctuations in plasma concentrations would affect the QTc interval duration.

Comparators

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, see Section 4.1); 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 (Zeldox briefing document 2000).

The doses of risperidone (prior to Amendment 2; see Section 4.1), quetiapine, and ziprasidone were based on recommendations from the manufacturers' Product Information.

Metabolic Inhibition

Two cytochrome P450 isoenzymes are primary participants in iloperidone metabolism. The first, CYP 3A4, causes demethylation of iloperidone to metabolite P88, which is found in only minute quantities in humans. Nevertheless, based on data from a single-dose drug interaction study, the addition of ketoconazole, a CYP3A4 inhibitor, to iloperidone resulted in modest (38-58%) increases in circulating levels of iloperidone and its metabolites P88 and P95 (internal report CILO522A0107 in preparation). The second isozyme, CYP2D6, catalyzes hydroxylation of the pendant acetyl group to form metabolite P94, which is converted to the metabolite P95 through a sequence of additional reactions. When fluoxetine, a 2D6 inhibitor, was given in combination with iloperidone in a single-dose drug interaction study, exposure (AUC) to iloperidone and metabolite P88 increased 131% and 119%, respectively (internal

report CILO522A0108 in preparation). No other P450 isoenzymes are significantly involved in iloperidone human metabolism.

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

ECG assessments

Large intraindividual variability in QTc duration has been described in the literature, with mean ranges within a day from 66 to 95 msec (Morganroth et al 1991, Molnar et al 1996, Pratt et al 1996). Various factors may contribute to this variability, including meals, circadian rhythm, and reader error (Molnar et al 1996, Nagy et al 1997). Several measures were taken to reduce variability in this study. 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.

Correction of QT

Many medications have chronotropic properties that influence QT duration. The duration of the QT interval is inversely related to heart rate; an increase in heart rate is usually associated with a lower QT duration. There are several formulas that are used for correction of QT measurements recorded from patients taking chronotropic medications. Of these, the Bazett ($QTcB = QT/(RR)^{1/2}$) and Fridericia ($QTcF = QT/(RR)^{1/3}$) formulas have been used most often. The FDA has also proposed a formula ($QTcD = QT/(RR)^{0.37}$) that is based on data across several psychotropic development programs. Another approach that has been used is to derive the exponent from a log-linear regression model based on ECG data at baseline (baseline correction). The analysis of the results of this study includes the corrected QTc values derived from all four formulas. The primary analysis was based on the Fridericia correction.

Duration of treatment

The study duration for each patient was dependent upon the titration regimen and time to reach steady-state concentrations for each medication.

Time to reach steady state for iloperidone and metabolites

The mean elimination half-life of iloperidone and its metabolites (P88 and P95) is approximately 24 hours. Steady-state concentrations are achieved within 5 days of dosing. Therefore, once the target dose was reached, patients were treated with iloperidone for 5 days before steady-state assessments were made.

Time to reach steady state for ziprasidone

The mean elimination half-life of ziprasidone is about 7 hours. Steady-state concentrations of ziprasidone are achieved within approximately 2 days of dosing. Therefore, once the target dose was reached, patients were treated with ziprasidone for 2 days before steady-state assessments were made.

Time to reach steady state for quetiapine

The mean elimination half-life of quetiapine is about 6 hours. Steady-state concentrations of quetiapine are achieved within 2 days of dosing. Therefore, once the target dose was reached, patients were treated with quetiapine for 2 days before steady-state assessments were made.

3.3 Study population

3.3.1 Patient population

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, and who were otherwise healthy and lived in the United States. The study was designed to include approximately 210 patients (changed to 175 based on Amendment 2; see Section 4.1) at 12 sites.

3.3.2 Inclusion and exclusion criteria

Inclusion criteria

Patients who met all of the following inclusion criteria at screening were eligible for enrollment in the study.

Patients included in the study were those:

- Male or non-fecund females (i.e., surgically sterilized or postmenopausal) between the ages of 18 and 65 years. Females of childbearing potential must have had a negative serum pregnancy test (β-hCG) at screening and agreement not to attempt to become pregnant during the course of the study. Additionally, the patient must have agreed to use contraceptive measures during the study.
- Cooperative, able to ingest oral medication, and willing and able to complete all aspects of the study.

- Able to provide written informed consent (or have a legally-authorized representative do so on their behalf) prior to participation in the study. (Following Amendment 1, the option to have a legally authorized representative provide consent was removed. See Section 4.1)
- Diagnosed (according to DSM-IV criteria) with schizophrenia subtypes 295.10 (disorganized), 295.20 (catatonic), 295.30 (paranoid), 295.60 (residual), or 295.90 (undifferentiated), or diagnosed with schizoaffective disorder (295.70)
- With no history or clinical evidence, as determined by the Investigator, of significant cardiovascular disease.

Exclusion criteria

Patients who met any of the following exclusion criteria at screening were not eligible for enrollment in the study.

Patients excluded from the study were those:

- Who suffered from a significant physical illness in the 4-week period preceding baseline.
- Who suffered from any clinically significant disease of the gastrointestinal system, liver, or kidneys, or any abnormal condition that compromised the function of these systems and could have resulted in the possibility of altered absorption, excess accumulation, or impairment of metabolism or excretion of the study medication.
- With other medical conditions which 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 ECG of the patient to a significant degree (e.g., severe obstructive lung disease, untreated thyroid disease, known HIV or hepatitis C infection, etc.) were excluded. This included any non-psychiatric coexistent disease state that had not been maintained in a stable condition for at least 3 months prior to baseline.
- With clinically significant abnormal laboratory finding that remains abnormal upon repeated measurement and that would put the patient at special risk, or significantly bias ECG assessments.
- With one or more of the following serological results: a positive hepatitis A antibody (anti-HAV IgM); a positive hepatitis B surface antigen (HBsAg); a positive hepatitis B core antibody (Anti-HBcAb), with a negative hepatitis B surface antibody (Anti-HBsAb), and abnormal liver enzymes or recent clinical symptoms of hepatitis (within the last 2 months).
- With a medical contraindication for oral treatment with iloperidone, quetiapine, ziprasidone or risperidone, such as hypersensitivity to the product. (Following Amendment 2, the risperidone treatment arm was removed. See Section 4.1 for details.)
- With a cardiovascular disease, if the patient had unstable angina, bypass surgery, a myocardial infarction, or angioplasty within 3 months.
- With an abnormal ECG at screening, defined as PR >240 msec, QRS complex >110 msec, QTcF >460, HR <50 or >110 (unless approved by sponsor), or any significant morphologic changes other than nonspecific T-wave changes.

- With second or third degree heart block; a history of clinically significant valve disorders; NYHA Class II-IV heart failure; dilated, restrictive, or hypertrophic cardiomyopathy; a history of significant cardiac arrhythmia or who were currently taking anti-arrhythmic medications; known congenital long QT syndrome.
- Who required medication known to inhibit or induce cytochrome P450 isoenzymes 2D6 or 3A4. Patients who received mood stabilizers or antidepressants (known to inhibit or induce these isoenzymes) within the past 2 weeks, fluoxetine within 5 weeks, depot fluphenazine within 4 weeks, or depot haloperidol decanoate within 6 weeks preceding baseline were excluded, unless the patient was documented to have a plasma concentration of that drug below the limit of quantitation.
- Who received medications that are known to increase QT interval duration or decrease QT interval duration (specifically β-blockers).
- Who received any experimental drug not approved for marketing in the U.S. during the 30 days immediately prior to screening.
- With a DSM-IV diagnosis of substance abuse or dependence within the past 3 months, or who were currently using illicit substances as determined by urine drug testing at screening.
- Who, in the opinion of the Investigator, were at risk of harming themselves or others (Amendment 1, 30-Nov-2001; see Section 4.1).

3.3.3 Interruption or discontinuation of treatment

It was noted on the eCRF whether or not each patient completed the study. If, for any patient, study treatment or observations were discontinued, the reason was recorded as follows:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. unsatisfactory therapeutic effect
5. subject's condition no longer requires study drug
6. protocol violation
7. patient withdrew consent
8. lost to follow up
9. administrative problems
10. death

Patients who prematurely withdrew from the study underwent, at the time of discontinuation (or within 24h thereafter), a complete assessment as would have been done at the endpoint had the patient completed the study. Patients who discontinued because of an AE, abnormal laboratory value, or abnormal test result were followed until resolution, or for 30 days,

whichever period was shorter, even if they were subsequently receiving treatment with another antipsychotic drug.

The Investigator was free to discontinue the patient's participation in the study if, in his/her judgment, continuation in the study may have proved harmful to the patient. Such a decision may have been precipitated by adverse events, including changes in vital signs, physical examination, ECG, or laboratory tests.

The Investigator maintained autonomy in making medical and safety decisions regarding the patient's continued participation in the trial. Clinically notable abnormalities in vital signs or laboratory tests, which may have guided clinical focus regarding a patient's continued participation included:

1. Vital sign abnormalities (e.g., sitting heart rate outside of the 50 - 120 b.p.m. range, or systolic blood pressure <90 or >180 mm Hg, or diastolic blood pressure <50 or >105 mm Hg) which proved persistent or changed in magnitude indicating a clinically significant risk to the patient's health, or
2. Elevations over 3 times the ULN for two or more of the liver function tests (AST/SGOT, ALT/SGPT, alkaline phosphatase, or bilirubin [>2 mg/dL]).

In addition, patients were free to discontinue from the study at any time, either by their own choice or that of their legal representative. If a patient elected to withdraw from the study, he/she was informed that it was extremely important that the reason for discontinuation be reported and that all end-of-study evaluations required by the protocol be performed. If a patient discontinued from the study, the IVRS was notified.

A patient for whom discontinuation was being considered for unsatisfactory therapeutic effect could have been switched to his/her usual treatment or any other available treatment.

3.4 Treatments

3.4.1 Investigational therapy and reference therapy

Investigational and reference drug was provided as tablets and supplied in bulk bottles. The pharmacist and/or study personnel at the site dispensed the appropriate medication to the patient.

Medication labels complied with the legal requirements and revealed no information about the patient.

The storage conditions for study drug were described on the medication label.

Investigational drug

The tablet strengths of iloperidone used in this study were 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, and 10 mg. The batch and formulation control numbers of all iloperidone strengths used are provided in Table 3-3.

Table 3-3 Iloperidone batch and formulation numbers

Product	Batch No.	Formulation No.
Iloperidone 1 mg tablets	F0450799	3752748.00.006
Iloperidone 2 mg tablets	F0261001	3752870.00.004
Iloperidone 4 mg tablets	F0480799	3752862.00.006
Iloperidone 6 mg tablets	F0291001	3752755.00.008
Iloperidone 8 mg tablets	F0140400	3752854.00.007
Iloperidone 10 mg tablets	F0150400	3758349.00.002

Reference therapy

The tablet strengths of quetiapine (supplied as Seroquel®) were 25 mg, 100 mg, 200 mg, and 300 mg. The capsule strengths of ziprasidone (supplied as Geodon®) used were 20 mg, 40 mg, 60 mg, and 80 mg. The batch and formulation numbers of all reference therapy used in this study are provided in Table 3-4.

Table 3-4 Reference therapy batch and National Drug Code (NDC) numbers

Product	Batch No.	National Drug Code No.
Risperidone 1 mg tablets	91P0743E	50458-0300-06
Risperidone 2 mg tablets	91P0850	50458-0320-06
Risperidone 3 mg tablets	91P0968E	50458-0330-06
Risperidone 4 mg tablets	91P1019	50458-0350-06
Quetiapine 25 mg tablets	3080H, 3675F	00310-0275-10
Quetiapine 100 mg tablets	3704F, 4690F	00310-0271-10
Quetiapine 200 mg tablets	3737F, 4508F	00310-0272-10
Quetiapine 300 mg tablets	3193H, 4523C	00310-0274-60
Ziprasidone 20 mg capsules	0326K01E, 0578K01D	0049-3960-60
Ziprasidone 40 mg capsules	0401K01D,	0049-3970-60
Ziprasidone 60 mg capsules	0414K01E, 0838K00F	0049-3980-60
Ziprasidone 80 mg capsules	0891K00D, 1132K01A	0049-3990-60

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

Metabolic inhibitors

The tablet strength of paroxetine (supplied as Paxil®) used in this study was 20 mg; the batch numbers were 20551B11 and 4540B11, NDC 00029-3211-20. The tablet strength of ketoconazole (supplied as Nizoral®) used in this study was 200 mg; the batch numbers were 91P0982E and 91P1006, NDC 50458-0220-10.

3.4.2 Treatment assignment

Randomization was performed using the Interactive Voice Response System (IVRS), a validated system that automates randomization to treatment groups. The randomization scheme was reviewed and approved by the Biostatistics Quality Assurance Group in the Novartis Medical Information Processing and Statistics Department. Randomization was stratified based on gender in order to assure equal distribution of males and females in each treatment arm. On Day -2, the Investigator called the IVRS prior to the morning assessments

to assign the patient to a treatment group. If a patient was randomized but did not receive study drug, the IVRS reassigned this treatment. The pharmacist dispensed the proper medication based on the dosing schedule (see Tables 3-5 and 3-6). The first dose was given at approximately 8 a.m. on Day 1.

Patient identification

Each screened patient received a patient number during the screening visit, which was the next available number at the site. This patient number remained the same throughout the study, and was used by the site to identify the patient. The patient identifier (ID) included a 4-digit center number (Center No.) and a unique patient number (Patient No.). This ID appears in the header at the top-center of each eCRF page.

Center No. - Novartis assigned a unique, 4-digit number to each center. This number was programmed into the center's software for the electronic data capture. If the Investigator had satellite sites, each subsite had a unique number.

Patient No. - Each patient was assigned a unique sequential number, starting with Patient No. 1 for the first patient at a given site. This number appeared in the Patient No. space on every eCRF for a given patient. If a patient discontinued from the study for any reason after having been assigned an ID, that ID was not reassigned. A patient's ID number remained the same for the patient throughout all phases of the study.

Dosing and dosing schedule

Tables 3-5 and 3-6 present the dosing schedules for iloperidone and the reference compounds, respectively.

Table 3-5 Dosing schedule for iloperidone

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

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

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

BOLD = Days of steady-state ECG evaluations

Table 3-6 Dosing schedule for reference therapies

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

TD = Target dose; P=paroxetine 20 mg q.d.; K=ketoconazole 200 mg b.i.d.
BOLD = Days of steady-state ECG evaluations

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

Dosing Instructions

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. All study medication was dispensed by study personnel.

Dosing instructions for metabolic inhibitors

During Periods 2 and 3, medications to inhibit CY450 drug metabolism were given. Paroxetine, ketoconazole, or both paroxetine and ketoconazole were administered dependent upon the treatment period and the treatment arm assignment (see Tables 3-5, 3-6). Paroxetine was administered in the morning at approximately 8:00 a.m. Ketoconazole was administered in the morning at approximately 8:00 a.m. and in the evening at approximately 6:30 p.m. On the last day of study drug administration, the evening dose of ketoconazole was not given (Amendment 2; see Section 4.1).

Food restrictions around T_{MAX} ECGs

On the days of ECG assessments (Days -2, -1, and 0, and Steady-State Days [SSD] 1, 2, and 3 of each treatment period), patients did not eat within 3 hours prior to, or during, the T_{MAX} ECG assessments. Therefore, patients randomized to either iloperidone or (prior to Amendment 2, see Section 4.1) 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®).

Dose skipping or interruption during the study

During the study, if any clinically relevant abnormal findings were observed (e.g., deviation of blood pressure or pulse rate, excessive sedation, etc.) the Investigator could have interrupted the patient's treatment according to the guidelines below. The reason for each missed dose was recorded in the eCRF.

During titration of study medications to the target dose

During titration of the study medications to the target dose, treatment interruption should not have exceeded 1 day (i.e., two consecutive doses during b.i.d. dosing or 1 dose during q.d. dosing) during the entire titration period. If treatment interruption occurred for one day, the dosing schedule was resumed unchanged. For example, if a patient had his/her Day 2 dose interrupted (a.m. and p.m. doses), the patient received the Day 2 medication on Day 3; if the Day 3 dose was interrupted (a.m. and p.m. doses), the patient received the Day 3 medication on study Day 4. In the case that dosing was further interrupted, the Investigator should have discussed the case with the Novartis Medical Monitor in order to ensure the safety and appropriateness of the patient's continued participation in the study.

After the target dose was reached

In the case that dosing was to be interrupted once the target dose was reached, the Investigator was instructed to discuss the case with the Novartis Medical Monitor in order to ensure the safety and appropriateness of the patient's continued participation in the study. If a subject

failed to receive target doses of iloperidone or (prior to Amendment 2; see Section 4.1) risperidone for 5 consecutive days, ziprasidone for 2 consecutive days or quetiapine for 2 consecutive days, the subject was considered unevaluable for PK/PD assessments. However, if the dose(s) were missed on the first day(s) of target dose administration, additional dosing days could have been added to the regimen in order to fulfill the requirement to reach steady state prior to PK/PD assessments. The Investigator should have discussed the case with the Novartis Medical Monitor to ensure appropriateness of additional dosing.

3.4.3 Blinding

This was an open-label study in which patients and Investigators were unblinded to treatment. As the primary outcome of this study was not likely to be influenced by the awareness of either Investigators or patients to treatment, blinding was not necessary. However, a centralized blinded ECG reader was used in order to avoid any potential bias in interpretation of ECG results.

3.4.4 Concomitant therapy

All concomitant illnesses were treated in accordance with prevailing medical practice. Medications known to inhibit or induce cytochrome P450 isoenzymes 2D6 and 3A4 (see Appendix 1.1) or known to increase QTc interval duration or decrease QTc interval (specifically beta-blockers) were not allowed.

Oral antipsychotic treatment taken prior to study enrollment must have been discontinued on or before Day -5. From Day -4 onward, the use of any antipsychotic medication other than the assigned study medication was not permitted.

In general, the use of other psychotropic agents was discouraged. However, below are the suggested medications in the event a patient experienced EPS, agitation, or insomnia.

Treatment of extrapyramidal symptoms (EPS)

Benztropine mesylate treatment could have been initiated for extrapyramidal symptoms.

Treatment of agitation or severe restlessness

Lorazepam could have been administered on a p.r.n. basis for the treatment of agitation or severe restlessness.

Treatment of insomnia

Zolpidem could have been used on a p.r.n. basis for the treatment of insomnia.

If any concomitant medication was initiated for any reason during treatment, this information was recorded on the concomitant medication eCRF page. Any medication taken before Day 1 was recorded on the prior/current medication eCRF page.

3.4.5 Treatment compliance

Records of study medication used and dosages administered were kept by the site pharmacist during the study. The pharmacist at each site dispensed each dose separately for each patient, and the dose was administered by study site personnel, thereby minimizing the influence of

poor compliance in this study. Study personnel also verified (by buccal examination) that the study medication had been swallowed.

Records of study medication used, dosages administered, and intervals between visits were kept during the study. Drug accountability was noted by the field monitor during site visits and at the completion of the trial. Patients were asked to return all unused medication at the end of the study.

3.5 Visit schedule and assessments

3.5.1 Visit schedule

Details for each of the study visits in this trial are provided in Table 3-7 (Pre-treatment phase) and Table 3-8 (Treatment phase). Some evaluations were recorded on the eCRFs, while others were retained in the patient's clinical record, transferred to a central facility via modem, or provided as printouts from a central facility. An eCRF Completion Guide describing how to complete each eCRF panel was provided to the sites.

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

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

[a] This Taper Period occurred in an outpatient setting. If deemed necessary by the Investigator, certain patients could undergo the Taper Period in an inpatient setting.

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

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

[d] Repeated at baseline only if the screening evaluations were performed more than 14 days before Day 0.

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

Table 3-8 Assessment schedule (Treatment phase)

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

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

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

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

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

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

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

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

[h] The IVRS was called to report patient completion or discontinuation.

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

[j] Three blood samples for pharmacokinetic analysis were drawn from patients in the iloperidone group.

[k] Performed only at premature discontinuation.

3.5.2 Efficacy assessments

No efficacy assessments were performed. However, the clinical status of patients was regularly assessed using the Severity of Illness scale of the Clinical Global Impression (CGI-S). Assessment was conducted at screening, baseline, and study completion or premature discontinuation, in order to obtain background information on severity of illness, and determine whether patients were discontinuing the study because of clinical worsening. These assessments were not intended to compare efficacy across treatments, but rather to confirm that the clinical status of all patients did not significantly deteriorate during this short-term study.

3.5.3 Safety assessments

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, monitoring of hematology, urinalysis, blood chemistry, vital signs, and performance of physical examinations and electrocardiograms.

Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory test or other means, was collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An Adverse Event (AE) is any undesirable sign, symptom or medical condition occurring after starting any medication or therapy used during the course of the study, even if the event is not considered to be related to that medication or therapy. "Study medication" or therapy included the Study Drug or therapy under evaluation, and any other reference drug, therapy or placebo administered during any phase of the trial.

Medical conditions or diseases present before starting study treatment were considered adverse events only if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment, but after signing the informed consent form, were recorded on the Medical History/Current Medical Conditions Case Report Form. Abnormal laboratory values or test results constituted adverse events only if the patient showed clinical signs or symptoms, or required therapy. The abnormal values or test results were then recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

As far as possible, each adverse event was also described by:

1. its duration (start and end dates),
2. the severity grade (mild, moderate, severe)
3. its relationship to the study drug (suspected / not suspected),
4. the action(s) taken and, as relevant, the outcome.

Serious adverse events

Information about all serious adverse events was collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event was reported

to Novartis within 24 hours of study site personnel learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. requires or prolongs hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition. This includes study procedures included in this protocol.
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- admission to a hospital or other institution for general care, not associated with any deterioration in condition
- treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission.

Any serious adverse event occurring after the patient had provided informed consent and until 4 weeks after the patient has stopped study participation was reported. This included the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during Washout Period, change in treatment to a fixed dose of concomitant medication). Serious adverse events that occurred more than 4 weeks after study discontinuation were only reported if a relationship to study drug (or therapy) was suspected.

Pregnancies

Any pregnancy that occurred during study participation was reported using a Clinical Trial Pregnancy Form. To ensure patient safety each pregnancy was also reported to Novartis within 24 hours of learning of its occurrence. The pregnancy was followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Laboratory evaluations

A central laboratory was used for this study. Any laboratory evaluation was repeated, if clinically indicated, and at the time of premature discontinuation. Details regarding the collection, shipment of samples, reporting of results, and alerting of extreme values were outlined in a laboratory manual, which was supplied to all sites.

Blood samples were collected for the following clinical laboratory evaluations:

Hematology

Hematological evaluations included: hemoglobin concentration, hematocrit, total and differential white blood cell count, and platelet count. Hematology evaluations were conducted at screening, baseline (only if screening evaluation was more than 14 days before Day 0), and study completion or premature discontinuation.

Blood chemistry

Blood chemistry evaluations included: blood urea nitrogen (BUN), uric acid, glucose, total protein, albumin, total bilirubin, total cholesterol, triglycerides, alkaline phosphatase, serum alanine aminotransaminase (ALT), serum aspartate aminotransaminase (AST), sodium, potassium, chloride, calcium, magnesium, inorganic phosphorous, bicarbonate, lactate dehydrogenase (LDH), creatinine, and creatine phosphokinase (CPK). Biochemistry evaluation was conducted at screening, baseline (only if screening evaluation was more than 14 days before Day 0), and study completion or premature discontinuation.

Urinalysis

Urinalysis evaluations included: specific gravity, pH, nitrites, protein, glucose, ketones, urobilinogen, bilirubin, leukocytes, casts, and blood. Urinalysis evaluations were conducted at screening, baseline (only if screening evaluation was more than 14 days before Day 0), and study completion or premature discontinuation.

Urine drug screen

A urine screen for drugs of abuse was performed at screening, baseline (only if screening evaluation was more than 14 days before Day 0), and study completion or premature discontinuation.

Pregnancy test

A pregnancy test was performed for females of childbearing potential at screening, baseline, and study completion or premature discontinuation. If a pregnancy test was positive, the patient's study medication was discontinued immediately and the Novartis CTL was contacted. The patient was followed to determine outcome.

Thyroid function test

A test for thyroid stimulating hormone (TSH) was carried out at screening only. If the serum concentration was found to be outside the normal range, the Novartis Medical Monitor was contacted for a decision on including the patient in the study.

Hepatitis screen

A hepatitis screen was carried out at screening only, and included assays for Hepatitis A antibody (IgM), Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb) and Hepatitis B core antibody (HBcAb).

Vital signs

Evaluation of vital signs consisted of the following:

- body temperature
- systolic and diastolic blood pressure
- radial pulse
- weight
- height

Measurements of systolic and diastolic blood pressure and radial pulse were taken after patients remained in a sitting position for 3 minutes.

Vital signs were measured at screening, b.i.d. on Days –2, -1, and 0, b.i.d. during all treatment periods, and once at study completion or premature discontinuation. Sitting blood pressure and radial pulse measurements were taken after the morning dose of study/reference medication and before the evening dose of study/reference medication. Weight was measured at screening, baseline, and study completion or premature discontinuation only. Height was measured at screening only.

Physical examination

All patients had a complete physical examination at screening. The physical exam was repeated at baseline only if the screening evaluations were performed more than 14 days before. The physical exam was repeated at study completion or premature discontinuation.

The evaluation included an examination of general appearance, ears, eyes, nose, throat, lungs, heart, abdomen, back, thyroid, lymph nodes, skin, extremities, and neurological exam.

Documentation of the physical examination must have been included in the patient's clinical record at the study site. Significant findings that were present prior to the start of study medication must have been recorded on the Relevant Medical History/ Current Medical Conditions Case Report Form. Significant findings that occurred after the start of study medication and that met the definition of an AE must have been recorded on the Adverse Events Case Report Form.

Clinical Global Impression of Severity (CGI-S)

The clinical status of patients was assessed using the Clinical Global Impression of Severity (CGI-S) scale. The 7-item CGI-S scale (Guy 1976) was developed to assess the overall, absolute degree of illness at any time. A rating of 1 is equivalent to "normal, not at all ill," and a rating of 7 is equivalent to "among the most extremely ill patients." The CGI-S was completed at screening, baseline, and study completion or at the time of premature discontinuation, and consistently referred to the degree of illness at the time of the evaluation and during the week prior to the visit.

ECG Assessments

A central facility was used in this study for interpretation and analysis of ECGs. ECG tracings were produced and transmitted via modem to the central ECG facility for interpretation by a blinded reader. A tracing was also printed at the site and retained in the patient's clinical record. Details concerning the ECG recording instructions were provided to all Investigators in a separate manual prior to the start of the study. The time the ECG was performed was recorded (using a 24h clock). The time that the patient took his/her last dose of study medication (prior to the ECG) was recorded on the eCRF page. Timing of ECGs used in primary analysis is dependent upon time for each compound to reach maximum concentration (T_{MAX}). Complete information regarding the optimal timing of ECG measurements for each compound is presented in the study protocol in Appendix 1.1 of this report.

3.5.4 Drug levels and pharmacokinetic assessments

Plasma samples for measurement of iloperidone and reference therapy concentration levels were collected on SSD1 and SSD2 of each period during the treatment phase. A "trough" blood sample was taken from all patients approximately 30 minutes before the a.m. dose of iloperidone or reference medication (i.e., approximately 7:30 am). Patients were instructed to take their morning dose of study medication as outlined in the dosing instructions in Section 3.4.2. The exact time of medication intake was recorded on the eCRF by study personnel. Plasma samples were collected at the estimated T_{MAX} for iloperidone (parent and primary active metabolite), quetiapine, and ziprasidone. For iloperidone-treated patients, one sample was collected at 2 hours post-dose, and one at 4 hours post-dose. For the reference compounds, quetiapine, and ziprasidone, one plasma sample was collected at 1 hour post-dose, 1.5 hours post-dose, and 6 hours post-dose, respectively. Plasma samples were then prepared for frozen shipment to the central laboratory. Detailed instructions on the handling and shipment of blood samples for pharmacokinetic analysis was provided separately to the Investigator.

In addition to timing the collection of samples for PK analysis according to the T_{MAX} of each compound, a consideration was given to collecting samples immediately after rather than before the ECG at that time in order to avoid discomfort of the patients and possible influences on the results of the ECG.

4 Protocol amendments, other changes in study conduct

4.1 Protocol amendments

Two amendments were made to the original protocol; both are provided in Appendix 1.1 of this report. Key changes are described below.

Amendment 1 (30-Nov-2001) modified the inclusion/exclusion criteria to (1) exclude patients who, in the opinion of the Investigator, were at risk of harming themselves or others, and to (2) remove the option for legally authorized representatives to provide informed consent, ensuring that only patients who could personally provide their consent were included in the study.

Amendment 2(09-Jan-2002) provided the following changes:

- The risperidone arm was removed from the study, to simplify study conduct by reducing the number of active comparators. The study was to continue with five arms instead of six, and the number of patients planned to participate in the study was reduced to approximately 175 to reflect the removal of the risperidone group.
- The PM dose of ketoconazole was not to be given on the last day of study drug administration. After careful review it was concluded that administering the PM dose of ketoconazole was unnecessary, as its physiological implications would not be realized until the following day. Since the collection of study data concluded on the last day of the study drug administration, it was unnecessary to administer the PM dose of ketoconazole.

In addition, Amendment 2 modified wording of the inclusion criteria to be consistent with the DSM-IV categorization of schizophrenia and schizoaffective disorder, and modified wording in the statistical methodology section to increase clarity. These changes are reflected in this report.

4.2 Other changes in study conduct

No other changes in study conduct occurred.

5 Data management

5.1 Data collection

Designated investigator staff entered the information required by the protocol into the Novartis Electronic Case Report Forms using a Novartis-supplied computer loaded with fully validated software that conforms to FDA requirements for electronic data capture. If a site experienced a hardware failure on Novartis-supplied computers, Novartis sent a replacement. Automatic validation programs checked for data discrepancies in the electronic Case Report Form and, by generating appropriate error messages, allowed modification or verification of the entered data before transfer to Novartis via a secure internet link. The Investigator certified that the data were complete and accurate by applying an electronic signature to the electronic Case Report Form and later received a CD-ROM or paper copies of the patient data for archiving at the investigational site. All electronic Case Report Forms sent to Novartis by investigational sites were reviewed upon receipt for any serious adverse events.

5.2 Database management and quality control

Data items were entered directly into the study database or indirectly from source data documents by designated Novartis-trained investigator staff using single data entry with electronic verification. Novartis staff reviewed the data for completeness and accuracy and instructed the site personnel to make any required corrections or additions. Queries were generally sent to the investigational site using an electronic data query system which provided an automatic audit trail of the corrections made by designated investigator staff. Occasionally, when queries were sent on a Data Query Form, the signed, original and resolved Data Query Form was kept at the investigator site and a copy sent to Novartis so the resolutions could be entered centrally into the database.

Concomitant medications entered into the database were coded using the WHO Drug Reference List which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Laboratory samples were processed centrally through Covance and the results were sent electronically to Novartis.

When the database was declared to be complete and accurate, the database was locked. Any changes to the database after that time could only be made by joint written agreement between the Clinical Trial Leader, the Trial Statistician and the Data Manager.

6 Statistical methods

6.1 Statistical methods

Data were analyzed by Novartis personnel.; detailed information is provided in Appendix 5.1. As described in Section 4.1, based on Amendment 2, the risperidone arm was removed from the study.

Primary QTc variable

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 1 (SSD1), Steady-State Day 2 (SSD2), and Steady-State Day 3 (SSD3) of Treatment Period 1 (without metabolic inhibitors).

Secondary QTc variables

- The QTc changes around T_{MAX} from baseline to the steady states of treatment periods 2 and 3. The baseline QTc value was obtained by averaging all QTc values around T_{MAX} on Days –2, -1, and 0. The QTc value at each steady state was obtained by averaging all QTc values around T_{MAX} on SSD1, SSD2, and SSD3 of the corresponding steady states during Treatment Periods 2 and 3, respectively.
- The QTc changes from baseline to steady state of treatment period 1. The baseline QTc value was obtained by averaging all fifteen QTc values on Days -2, -1, and 0. The QTc value at the steady state was obtained by averaging all fifteen QTc values on SSD1, SSD2, and SSD3 of Treatment Period 1.
- The QTc changes from Day 0 to SSD3 of Treatment Period 1. The QTc value at Day 0 was calculated by averaging all nine QTc values on Day 0. The QTc value on SSD3 of treatment period 1was calculated by averaging all nine QTc values on that day.
- The QTc changes at different times of day (morning, afternoon, and evening) from Day 0 to SSD3 of Treatment Period 1. The morning QTc values were calculated by averaging

the three morning QTc values on Day 0 and on SSD3 of treatment period 1, respectively. Noon and evening values were calculated in the same manner as described above.

- Incidence of QTc increase around T_{MAX} ≥30 msec from baseline to each of the three steady states. The baseline QTc value was obtained by averaging all QTc values around T_{MAX} on Days –2, -1, and 0. Multiple incidences for each patient within each steady state were counted only once.
- Incidence of QTc increase around T_{MAX} ≥60 msec from baseline to each of the three steady states. The baseline QTc value was obtained by averaging all QTc values around T_{MAX} on Days –2, -1, and 0. Multiple incidences for each patient within each steady state were counted only once.
- Incidence of QTc values around T_{MAX} ≥500 msec at baseline and at each of the three steady states. Multiple occurrences within baseline and each steady state for a patient were counted only once.

It was planned that the data from all centers that participated in this protocol would be combined, so that data from an adequate number of patients would be available for analysis.

Analysis methods

Data for all the primary and secondary QTc variables were summarized by treatment groups and by steady state of treatment period. Ninety-five percent confidence intervals were constructed for the mean QTc change around T_{MAX} for each treatment group and by steady state.

An analysis of covariance was performed on the primary QTc variable for both the primary and secondary QTc populations with adjusted baseline QTc values as the covariate and treatment and gender as class variables. Each patient's baseline QTc value was obtained by averaging all QTc assessments around T_{MAX} on Days –2, -1, and 0. The adjusted baseline QTc value for each patient was then obtained by subtracting the mean of all the original baseline values around T_{MAX} for all patients from that patient's baseline QTc value. Ninety-five percent confidence intervals were constructed based on the above model for the primary QTc variable for each of the treatment groups. Subgroup summary statistics were also provided for the primary QTc variable by gender.

QTc correction factors

The QTc correction calculation was based on the formula $QTc=QT/RR^c$, where c denotes the correction factor. All four corrections (Bazett, Fridericia, FDA, and Baseline) were used for calculating QTc intervals. The Baseline correction was obtained by regressing log (RR) on log (QT) using baseline ECG data. The baseline values for QT and RR were obtained by averaging all available QT and RR values at baseline for each patient. The coefficient for log(QT) from the regression analysis was used as the correction.

6.1.1 Populations

Primary QTc population The primary patient population for the QTc analysis included all patients who had at least 50% (≥5) of the QTc evaluations on days SSD1, SSD2, and SSD3 at

T_{MAX} during Treatment Period 1 and at least half (≥5) of the QTc evaluations around times that corresponded to the T_{MAX} for each compound at baseline (Days –2, -1 and 0).

Secondary QTc population This population included all patients who had at least one QTc assessment at baseline (Days -2, -1, and 0) and at least one QTc assessment post-baseline at any of the three steady-states.

Safety population: The safety population included all randomized patients who took at least one dose of study medication and had at least one post-baseline safety evaluation.

6.1.2 Background and demographic characteristics

Appropriate summary statistics for the baseline demographic and psychiatric profile variables are provided by treatment group for all randomized patients. Age was calculated based on the date from the demographic CRF page. Baseline CGI-S assessments were included in these summaries to indicate psychiatric illness severity. Summary statistics for the baseline variables by treatment group were presented in a post-text table. P-values resulting from a comparison of the treatment group homogeneity with respect to these variables are also presented. These p-values are provided for descriptive purposes only. The p-values addressing treatment group comparability were presented in Appendix 5.1. Additionally, screening failures and randomized patients were summarized by age, sex, and race.

6.1.3 Study medication

The duration of exposure to study medication was summarized for all randomized patients.

6.1.4 Concomitant therapy

Concomitant medications/therapies (medications/therapies present at the first dose of study medication and/or thereafter that could have been present before the first dose of study medication) were recorded throughout the study and at early termination. However, for the purpose of analysis, concomitant medications/therapies were defined as those taken after the first dose of study medication. Concomitant medications and newly occurring concomitant medications (i.e., concomitant medications that were not present before the first dose of study medication but were initiated thereafter) were summarized. Past medications/therapies including psychotropic use (medications/therapies that were present before the first dose of study medication that could have been present thereafter) were recorded at screening. All medications were coded using the WHO-DRL dictionary. Medications were coded to a unique Novartis drug code (NDGCODE1A) with an associated preferred term. These codes were then merged onto the WHOATC dictionary (by NDGCODE1A) to assign drug classes. There may be multiple ATC class assignments for one drug.

The number of patients using prior or concomitant medications are categorized by WHOATC drug class, and preferred term, and presented for each treatment group. (Note: In any given drug class, a patient was counted only once).

6.1.5 Efficacy evaluation

Efficacy was not evaluated in this study.

6.1.6 Safety evaluation

In addition to the evaluation of QTc changes described in Section 6.1, the assessment of safety was based on treatment-emergent AEs, vital signs, laboratory values and ECG evaluations.

Adverse events and medical conditions

Adverse events were recorded throughout study and at early termination. Adverse events and medical conditions were coded using the MedDRA coding dictionary. Treatment emergent adverse events were defined as those events that were newly occurring or worsening from baseline (i.e., adverse event start date is greater than Day 0). In all cases, only treatment emergent adverse events are summarized.

Treatment emergent adverse events are summarized by presenting, for each treatment group, the number and percentage of patients having any treatment emergent adverse event, having an adverse event in each body system, and having each individual adverse event. (Note: In any given category [e.g., body system] a patient is only counted once). Similar displays are provided for prior (conditions ending prior to the first dose of study medication) and current medical conditions (conditions present while on study medication).

Information is further categorized by severity, drug relationship, concomitant medication taken and treatment period. Other information collected is listed as appropriate.

Serious adverse events (SAEs) were collected any time during the study up to 4 weeks after the last dose of study medication. SAEs (including death) are provided in a tabular format.

Vital sign, ECG, and laboratory data

For vital signs, summary statistics (means, medians, standard deviations, ranges) and change from baseline of blood pressures and pulse were presented by day for each treatment. The proportion of patients with clinically notable abnormalities as defined in Post-text Supplement 1 is also summarized by treatment period for each treatment. The baseline value was obtained by averaging all values for Days –2, -1, and 0. Summary statistics at endpoint and change from baseline of weight and body temperature were also produced. The proportion of patients with clinically notable abnormalities as defined in Post-text Supplement 1 is also summarized overall for each treatment.

All ECG-related raw data and change from baseline are summarized by treatment period for each treatment group. The baseline value was obtained by averaging all assessments for Days -2, -1, and 0. Newly occurring or worsening ECG abnormalities (as determined by the central ECG laboratory) are also summarized by treatment group.

Laboratory data and change from baseline are summarized at endpoint for each treatment. The proportion of patients with clinically notable abnormalities (see Post-text Supplement 1 for definition) is also summarized overall for each treatment. The proportion of patients with values outside the extended normal range is presented. Data are also summarized by presenting shift tables using extended normal range.

6.1.7 Interim analyses

No interim analyses were planned or performed.

6.1.8 Other topics

Pharmacogenetic data analysis

The exploratory pharmacogenetic study was designed to investigate the association between genotypes and phenotypes. Neither genotypes nor phenotypes were pre-specified for this investigation. Hence, all statistical analyses performed are considered exploratory. Summary statistics will be performed by the Novartis pharmacogenetics group and the correlation between the genotype and phenotype will be assessed. Other statistical methods used in genetic studies may have been used for exploring this relationship, if applicable. Due to multiple comparisons of unspecified hypotheses, results of applied test procedures serve illustrative purposes only.

If the numbers of subjects enrolled in the study were too small to complete proper statistical analyses, these data were combined, as appropriate, with those from other studies to enlarge the data set for analysis. These pharmacogenetic analysis will be summarized in a separate report.

Pharmacokinetic analysis

The relationship between plasma concentration and QTc was investigated with an analysis of covariance (ANCOVA) approach. In the analysis, the mean QTc and concentration values around T_{MAX} were the response and the main explanatory variables, respectively, with mean baseline QTc adjustment. This analysis was performed for all the treatment periods and for all the treatment groups where PK samples were collected.

6.2 Sample size and power considerations

The sample size of the study was calculated according to inter- and intra-patient variations based on the results found with patients enrolled in earlier iloperidone studies. Both inter- and intra-patient standard deviations of QTc change were expected to be 14 msec or less. Multiple evaluations per patient were expected to control the overall between-patient standard deviation to within 16 msec. Twenty-eight patients per group allowed a 95% confidence interval for the mean QTc change to be constructed with a width of 12 msec (mean±6 msec). A total of 35 patients per treatment arm were to be randomized to provide at least 28 patients per group with a sufficient number of ECG evaluations for the calculation.

7 Patients studied

7.1 Patient disposition

A total of 242 patients were screened; of these, 188 patients were randomized to receive study drug (5 patients were randomized to risperidone - this arm was removed following Amendment 2, dated 9-Jan-02).

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%).

The completion rate was similar across treatment groups. The most common reason for discontinuation in any group was withdrawal of consent. The disposition of the 188 patients who were randomized and the primary reason for discontinuation are summarized in Table 7-1. Detailed information for each patient is presented in Post-text Listing 7.1-1.

Table 7-1 Patient disposition by treatment group (All randomized patients)

	ILO 8 mg b.i.d.	ILO 12 mg b.i.d.	ILO 24 mg q.d.	RIS 8 mg b.i.d.	ZIP 80 mg b.i.d.	QUET 375 mg b.i.d.	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients randomized	39	39	35	5	35	35	188
Patients Received study drug	34 (87)	37 (95)	35 (100)	5 (100)	34 (97)	35 (100)	180(96)
Patients Completed study	25 (64)	29 (74)	29 (83)	4 (80)	30 (86)	32 (91)	149(79)
Patients Discontinued	14 (36)	10 (26)	6 (17)	1 (20)	5 (14)	3 (9)	39 (21)
Discontinuations:							
Treatment emergent AEs	3 (8)	2 (5)	1 (3)	0 (0)	1 (3)	1 (3)	8 (4)
Unsatisfactory Therapeutic Effect	1 (3)	2 (5)	0 (0)	0 (0)	2 (6)	0 (0)	5 (3)
Protocol Violation	2 (5)	0 (0)	0 (0)	1 (20)	0 (0)	1 (3)	4 (2)
Withdrawal of Consent	8 (21)	6 (15)	5 (14)	0 (0)	2 (6)	1 (3)	22 (12)

242 patients screened

ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine; RIS=risperidone

Note: Investigator determined primary reason for discontinuation. Only one reason was recorded on Case Report Form.

Source: Post-text table 7.1-1

7.2 Protocol deviations

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). Other deviations from the protocol were minor in nature and generally involved missed procedures or timing of procedures. Sponsor-approved protocol deviations were recorded systematically in the patient study documentation and are available upon request.

7.3 Groupings for analysis

Of the 180 patients that were randomized and received study medication, 163 patients had at least one-half of the QTc evaluations (≥5 ECGs) on SSD1, SSD2, and SSD3 at T_{MAX} during Treatment Period 1 and at least one-half of the QTc evaluations (≥5 ECGs) around times that corresponded to the T_{MAX} for each compound at baseline (Days –2, -1 and 0) and were included in the primary QTc population (Table 7-2).

One-hundred sixty-five patients had at least one QTc evaluation at baseline (Days –2, -1 and 0) and had at least one QTc evaluation post-baseline at steady state with or without metabolic inhibitor and were included in the secondary QTc population.

All of the 180 patients who were randomised and received study medication had at least one post-baseline safety assessment and were included in the safety population.

Table 7-2 Number of patients in analysis populations by treatment group

	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.	Total
	N=39	N=39	N=35	N=35	N=35	N=188
Population	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients receiving study medication	34 (87)	37 (95)	35 (100)	34 (97)	35 (100)	180 (96%)
Safety Population [a]	34 (87)	37 (95)	35 (100)	34 (97)	35 (100)	180 (96%)
Primary QTc population [b]	28 (72)	34 (87)	31 (89)	32 (91)	33 (94)	163 (87%)
Secondary QTc population [c]	29 (74)	34 (87)	31 (89)	33 (94)	33 (94)	165 (88%)

ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine

Source: Post-text table 7.3-1

7.4 Baseline demographic and background characteristics

Baseline demographic and background information were similar across all treatment groups (risperidone group is not summarized). Demographic and background information is listed for each patient in Post-text Listing 7.4-1.

A total of 242 patients were evaluated for participation in this study with 54 patients failing the screening procedures. The most common reason for screening failure was unacceptable laboratory value(s) (18/54). Other common reasons included withdrawal of consent (11/54), other (11/54), and unacceptable test procedure (8/54) (Post-text Listing 7.2-1). Demographic information for patients screened but not randomized (i.e., "screening failures") is provided in Post-text Table 7.2-1.

Table 7-3 Demographic and background summary by treatment group (All randomized patients)

		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=39	N=39	N=35	N=35	N=35
Age (years)	N	39	39	35	35	35
	Mean (± SD)	41.4 (± 8.7)	41.2 (± 8.3)	38.8 (± 8.5)	40.3 (±7.8)	39.3 (± 7.3)
Age (years)	n(%)					
	18-24	2 (5)	1 (3)	3 (9)	1 (3)	0 (0)
	25-44	21 (54)	22 (56)	22 (63)	20 (57)	26 (74)
	45-65	16 (41)	16 (41)	10 (29)	14 (40)	9 (26)
Sex	N (%)					
	Male	28 (72)	28 (72)	25 (71)	25 (71)	25 (71)
	Female	11 (28)	11 (28)	10 (29)	10 (29)	10 (29)
Race	N (%)					
	Caucasian	16 (41)	19 (49)	19 (54)	16 (46)	13 (37)
	Black	16 (41)	17 (44)	12 (34)	17 (49)	13 (37)
	Oriental	1 (3)	0 (0)	1 (3)	1 (3)	0 (0)
	Other	6 (15)	3 (8)	3 (9)	1 (3)	9 (26)
DSM-IV criteria	N (%)					
	20	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)
	30	27 (69)	28 (72)	20 (57)	22 (63)	24 (69)
	60	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)
	70	9 (23)	11 (28)	9 (26)	10 (29)	9 (26)
	90	1 (3)	0 (0)	6 (17)	2 (6)	2 (6)
Baseline CGI-S	N	33	37	34	33	33
	Mean (± SD)	3.5 (±0.7)	3.5 (±0.7)	3.4 (± 0.7)	3.5 (±0.8)	3.5 (± 0.7)

ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine; CGI-S=Clinical Global Impression of Severity

Source: Post-text table 7.4-1, Post-text table 10.5-3

Past medical conditions were reported for 68% of all randomized patients (Post-text Table 7.4-2). The most commonly occurring past medical conditions (≥ 5%) were head injury (7%) and headache (7%).

Current medical conditions were reported for 95% of all randomized patients (Post-text Table 7.4-3). The most commonly occurring current medical conditions (≥ 5%) were insomnia (44%), anxiety (42%), headache (35%), drug hypersensitivity (17%), dyspepsia (14%), hypertension (14%), GERD (11%), back pain (9%), constipation (7%), arthralgia (7%), depression (7%), agitation (6%), obesity (6%), acquired hypothyroidism (5%), arthritis (5%), migraine (5%), allergic rhinitis (5%), and scar (5%).

No clinically important differences were observed among treatment groups with respect to the percentage of patients with past or current medical conditions. More detailed information on patients with past or current medical conditions in presented in Post-text Listing 7.4-2.

Prior medications or therapies (defined as any medication taken before the start of study medication) were reported for 99% of all randomized patients (Post-text Table 7.4-4b). The

most commonly occurring (≥5%) prior medications/therapies were lorazepam (62%), zolpidem (57%), olanzapine (35%), risperidone (31%), paracetamol (29%), quetiapine (20%), benztropine (19%), ibuprofen (16%), diphenhydramine (10%), valproic acid (10%), haloperidol (10%), multivitamins (10%), acetylsalicylic acid (8%), trazodone (7%), paroxetine (7%), lithium (6%), mylanta (5%), amlodipine (5%), salbutamol (5%), sertraline (5%), citalopram (5%), and levothyroxine (5%). More detailed information on patients with prior medications/therapies is presented in Post-text listing 7.4-5.

Prior psychotropic medication (defined as any antipsychotic, mood stabilizer, anxiolytic, antidepressant, or sedative) received within 30 days prior to start of study medication were reported for 90% of all randomized patients (Post-text Table 7.4-4a). The most commonly occurring prior psychotropic medications (≥5%) were lorazepam (45%), zolpidem (43%), olanzapine (32%), risperidone (28%), quetiapine (18%), valproic acid (8%), haloperidol (6%), trazodone (6%), paroxetine (6%) and citalopram (5%). More detailed information on patients with prior medications/therapies is presented in Post-text listing 7.4-5.

8 Medication

8.1 Study medication

8.1.1 Dosage

Study medication was administered according to the dosing regimen specified in the protocol. The number of patients with dose interruptions (defined as any change in study medication not specified in the protocol) is summarized in Post-text Table 8.1-4. Dose interruptions were not permitted after the target dose was reached and before ECG assessments were conducted. Therefore, dose interruptions in this study occurred either during dose escalation or after ECG assessments were conducted. More detailed information concerning dosing is presented in the Drug Administration Record listing (Post-text Listings 8.1-1 and 8.1-2).

8.1.2 Patient exposure

The expected duration of exposure is dependent upon treatment group assignment. Patients randomized to iloperidone 8 mg b.i.d., iloperidone 12 mg b.i.d., iloperidone 24 mg qd, ziprasidone 80 mg b.i.d., and quetiapine and completing the study received treatment for 28, 30, 31, 21, 15, and 17 days, respectively. Duration of exposure is presented by treatment group in Table 8-1. Cumulative duration of exposure is presented in Post-text Table 8.1-2. Duration of exposure is presented by Treatment Period in Post-text Table 8.1-3.

Table 8-1 Duration of exposure by treatment group (All randomized patients)

	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=39	N=39	N=35	N=35	N=35
	n (%)	n (%)	n (%)	n (%)	N (%)
Day					
1-7	3 (8)	0 (0)	0 (0)	1 (3)	2 (6)
8-14	3 (8)	3 (8)	3 (9)	3 (9)	1 (3)
15-21	2 (5)	3 (8)	1 (3)	30 (86)	32 (91)
22-28	24 (62)	1 (3)	1 (3)	0 (0)	0 (0)
≥29	2 (5)	30 (77)	30 (86)	0 (0)	0 (0)
Never received study medication	5 (13)	2 (5)	0 (0)	1 (3)	0 (0)

ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine

Source: Post-text Table 8.1-1

8.1.3 Drug level and pharmacokinetic data

Drug level and pharmacokinetic data are presented in conjunction with pharmacodynamic evaluations in Section 9.3.

8.2 Concomitant medication

Concomitant medications or therapies were reported for 92% of all randomized patients. The most commonly occurring concomitant medications (≥ 5%) were lorazepam (73%), zolpidem (69%), paracetamol (49%), mylanta (21%), ibuprofen (19%), benzatropine (13%), diphenhydramine (10%), guaifenesin (9%), magnesium chloride (9%), cetylpyridinium (8%), chloral hydrate (6%), hydrocortisone (5%), amlodipine (5%), sodium chloride (5%), docusate (5%), pseudoephedrine (5%), and levothyroxine (5%) (Post-text Table 8.2-1).

Newly occurring concomitant medications or therapies (defined as any medication/therapy present from start of study medication onward that was not present in the pre-treatment phase) were reported for 77% of all randomized patients. The most common newly occurring medications (≥ 5%) were paracetamol (26%), lorazepam (19%), zolpidem (19%), mylanta (17%), benzatropine (10%), ibuprofen (9%), magnesium hydroxide (7%), diphenhydramine (6%), cetylpyridinium (6%), and guaifenesin (5%) (Post-text Table 8.2-2).

9 QTc analysis results

The primary and secondary analyses in this study evaluated the effects of iloperidone on QTc interval duration; results are presented in Sections 9.1, 9.2, and 9.3.

9.1 Primary QTc analysis

The primary variable for QTc was the change from baseline to steady state in the QTcF (Fridericia) at T_{MAX} during Treatment Period 1.

The mean change from baseline in QTcF was similar for iloperidone 8 mg b.i.d. (8.5±10.5 msec), iloperidone 12 mg b.i.d. (9.0±12.5 msec), and ziprasidone 80 mg b.i.d (9.6±11.0 msec). Quetiapine 375 mg b.i.d. (1.3±11.1 msec) was associated with the smallest mean change from baseline at Tmax in QTcF and iloperidone 24 mg q.d. (15.4±11.7 msec) was associated with largest mean change from baseline (Table 9-1). Mean changes in the primary QTc variable using the FDA and baseline correction factor (0.3351) were similar to results obtained using the Fridericia's correction factor. Mean changes using the Bazett's correction factor were higher in all treatment groups and were most different from results obtained using the other correction formulas for compounds with the greatest influence on heart rate (i.e. quetiapine and iloperidone b.i.d.) (Table 10.9).

An analysis of covariance (ANCOVA) was performed on the primary QTc variable with adjusted baseline QTc values as the covariate and treatment and gender as class variables. Least square mean changes based on the ANCOVA model did not differ substantially from raw mean values and are summarized in Post-text table 9.2.1-2.

Mean QTcF changes including 95% confidence intervals from baseline to steady state at T_{MAX} during treatment period 1are illustrated in Figure 9-1.

Table 9-1 Summary statistics of QTc change (95% CI) from baseline to steady state at T_{MAX}* during Treatment Period 1 (Primary QTc population)

	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.
Baseline					
N	28	34	31	32	33
Mean ± SD (Fridericia)	385.9 ± 16.4	386.5 ± 17.1	379.0 ± 14.7	383.4 ± 13.5	383.2 ± 18.9
Mean ± SD (Baseline)	385.9 ± 16.4	386.5 ± 17.2	379.0 ± 14.7	383.6 ± 13.5	383.3 ± 19.0
Mean ± SD (FDA)	388.2 ± 16.1	389.5 ± 17.8	381.1 ± 14.4	386.3 ± 13.5	385.9 ± 19.3
Mean ± SD (Bazett)	396.7 ± 17.5	400.7 ± 22.1	388.8 ± 15.8	396.5 ± 16.5	395.6 ± 22.9
Change in QTc (Tx Period 1)					
N	28	34	31	32	33
Mean ± SD (Fridericia)	8.5 ± 10.5	9.0 ± 12.5	15.4 ± 11.7	9.6 ± 11.0	1.3 ± 11.1
Mean ± SD (Baseline)	8.7 ± 10.5	9.0 ± 12.6	15.4 ± 11.6	9.6 ± 11.0	1.4 ± 11.1
Mean ± SD (FDA)	10.2 ± 10.8	10.4 ± 12.4	16.3 ± 11.8	10.7 ± 11.1	3.7 ± 11.3
Mean ± SD (Bazett)	16.0 ± 13.7	15.6 ± 13.9	19.3 ± 14.8	14.7 ± 12.8	12.6 ± 14.2

N=number of patients; ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine

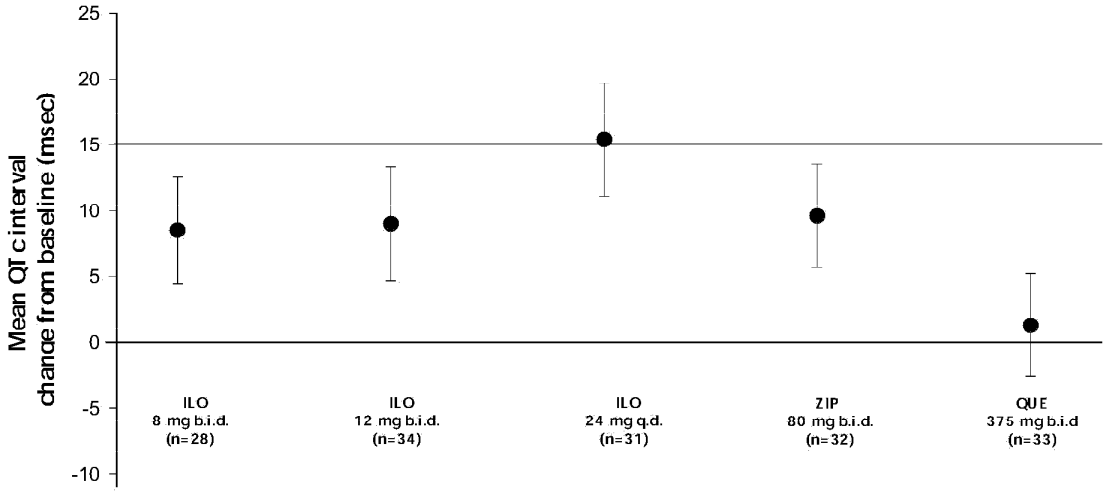
Tx=Treatment

*T_{MAX}=estimated time of maximum concentration (ILO = 2-4 hours post-dose; ZIP = 5-7 hours post-dose; QUET = 1-2.5 hours post-dose).

Note: Baseline QTc value obtained by averaging all QTc assessments on Days –2, -1 and 0 that correspond with T_{MAX} for each compound. Steady state QTc value was obtained by averaging all QTc assessments around T_{MAX} on Days SSD1, SSD2 and SSD3 during the first treatment period.

Source: Post-text Table 9.1-1

Figure 9-1 Mean QTc (Fridericia) change (95%CI) from baseline to steady state at T_{MAX}* during Treatment Period 1 (Primary QTc population)



ILO=iloperidone; ZIP=ziprasidone; QUE=quetiapine
Note: * T_{MAX} = estimated time of maximum concentration (ILO=2-4 hours post-dose; ZIP=5-7 hours post-dose; QUET= 1-2.5 hours post-dose)
Baseline QTc value obtained by averaging all QTc assessments on Days –2, -1 and 0 that correspond with T_{MAX} for each compound. First steady state QTc value is obtained by averaging over all QTc assessments around T_{MAX} on Days SSD1, SSD2, and SSD3 for the first steady state.
Source: Post-text Figure 9.1-1

Post-text Table 9.1-3 presents a summary of QTc change from baseline to steady state at T_{MAX} during treatment period 1 by gender for the primary QTc population. Female patients were equally distributed amongst the treatment groups with 8, 10, 9, 8 and 9 females randomized to iloperidone 8 mg b.i.d., iloperidone 12 mg b.i.d., iloperidone 24 mg q.d., ziprasidone 80 mg b.i.d, and quetiapine 375 mg b.i.d. respectively. Mean QTcF change for female patients was 10.6±15.5 msec, 3.0±12.9 msec, 18.1±11.8 msec, 6.0±9.8 msec, and -1.6±12.3 msec for iloperidone 8 mg b.i.d., iloperidone 12 mg b.i.d., iloperidone 24 mg q.d., ziprasidone 80 mg b.i.d, and quetiapine 375 mg b.i.d, respectively. Mean QTcF change for male patients was 7.6±8.0 msec, 11.4±11.7 msec, 14.3±11.7 msec, 10.8±11.3 msec, and 2.4±10.7 msec for iloperidone 8 mg b.i.d., iloperidone 12 mg b.i.d., iloperidone 24 mg q.d., ziprasidone 80 mg b.i.d, and quetiapine 375 mg b.i.d, respectively.

9.2 Secondary analysis of QTc interval

The main secondary QTc variables of interest included the mean change from baseline to steady state at T_{max} during treatment period 1, 2, and 3, the incidence of increases in QTc of ≥30 and 60 msec from baseline to steady state at T_{max}, and the incidence of QTc values of ≥ 500 msec at baseline or during any of the three treatment periods.

Additional variables of interest included the mean change from Day 0 to SSD3 of Treatment Period 1 (9 ECGs over the course of the day on both Day 0 and SSD3), mean change in QTc

at different times of the day from Day 0 to SSD3 of Treatment Period 1 (morning, afternoon, evening), and the mean change from baseline to steady state during Treatment Period 1 including all ECGs (15 ECGs over 3 days at baseline and 15 ECGs at steady state during Treatment Period 1).

An analysis of patients with ECG measurements that revealed QTcF increases from baseline to steady state of ≥60 msec at T_{max} or QTcF values ≥ 500 msec for all treatment periods was performed. Baseline is defined as the average of all QTcF values on Study Days –2, -1 and 0 that correspond to T_{max} for each compound. A total of 7 patients (all Iloperidone patients) showed ECG measurements with QTcF increases of ≥60 msec from baseline.

A second analysis was performed to identify outlier patients with QTcF increases from baseline to steady state Day 3 of ≥60 msec or QTcF values ≥ 500 msec at Treatment Period 1. Baseline is defined as the average of QTcF values on Day 0 of the baseline period. One Iloperidone (8 mg/d) patient, not identified in the first analysis, met this abnormality criteria.

A third analysis approach was performed to identify all outlier patients with QTcF increases from baseline to steady state of ≥60 msec or QTcF values ≥ 500 msec during Treatment Period 1. Baseline is defined as the average of QTcF values on Study Days –2, -1 and 0 (comprising all values). Two additional patients (from the Iloperidone 8 mg/d treatment group) were determined to have a QTcF increases of ≥60 msec from baseline.

9.2.1 Mean change in QTc from baseline to steady state at Tmax during treatment period 1, 2, and 3

During Treatment Period 1, the results for mean change in QTcF from baseline to steady state at T_{max} do not differ substantially from results obtained using the primary population (Table 9-2 .

During Treatment Period 2 (the presence of one metabolic inhibitor), the mean change from baseline in QTcF was highest in the iloperidone 24 mg q.d. (17.5±10.3 msec) and ziprasidone 80 mg b.i.d. (15.9±11.8 msec) groups, followed by the iloperidone 8 mg b.i.d. (11.2±12.0 msec) and iloperidone 12 mg b.i.d. (11.6±16.8 msec) groups. The smallest mean change from baseline at T_{max} during Treatment Period 2 was observed in the quetiapine 375 mg b.i.d. (2.6±11.5 msec) group (Table 9-2 . In comparison to Treatment Period 1, the mean change from baseline in QTcF at T_{max} was numerically higher in all treatment groups. The percentage increase from Treatment Period 1 to Treatment Period 2 in QTcF at T_{max} was greatest in the ziprasidone (60%) and quetiapine (50%) arms followed by the iloperidone 12 mg b.i.d. (29%) and iloperidone 8 mg b.i.d. (26%) treatment arms. The smallest percentage increase in QTcF at T_{max} from Treatment Period 1 to Treatment Period 2 was observed in the iloperidone 24 mg q.d. group (14%).

During Treatment Period 3 in which a second metabolic inhibitor was added to the regimen of only iloperidone-treated patients, the mean change in QTcF from baseline to steady state at T_{max} was highest in the iloperidone 24 mg q.d. (19.5±11.9) groups and iloperidone 12 mg b.i.d. (19.3±17.1), followed by the iloperidone 8 mg b.i.d. (15.7±14.1) group (Table 9-2 . The percentage increase in QTcF at T_{max} from Treatment Period 2 to Treatment Period 3 was greatest in the iloperidone 12 mg b.i.d. group (66%), followed by the iloperidone 8 mg b.i.d. (40%), and the iloperidone 24 mg q.d. (11%) groups, respectively.

Mean QTcF changes from baseline to steady state at T_{max} including 95% confidence intervals during Treatment Periods 1, 2 and 3 are illustrated in Figure 9-2.

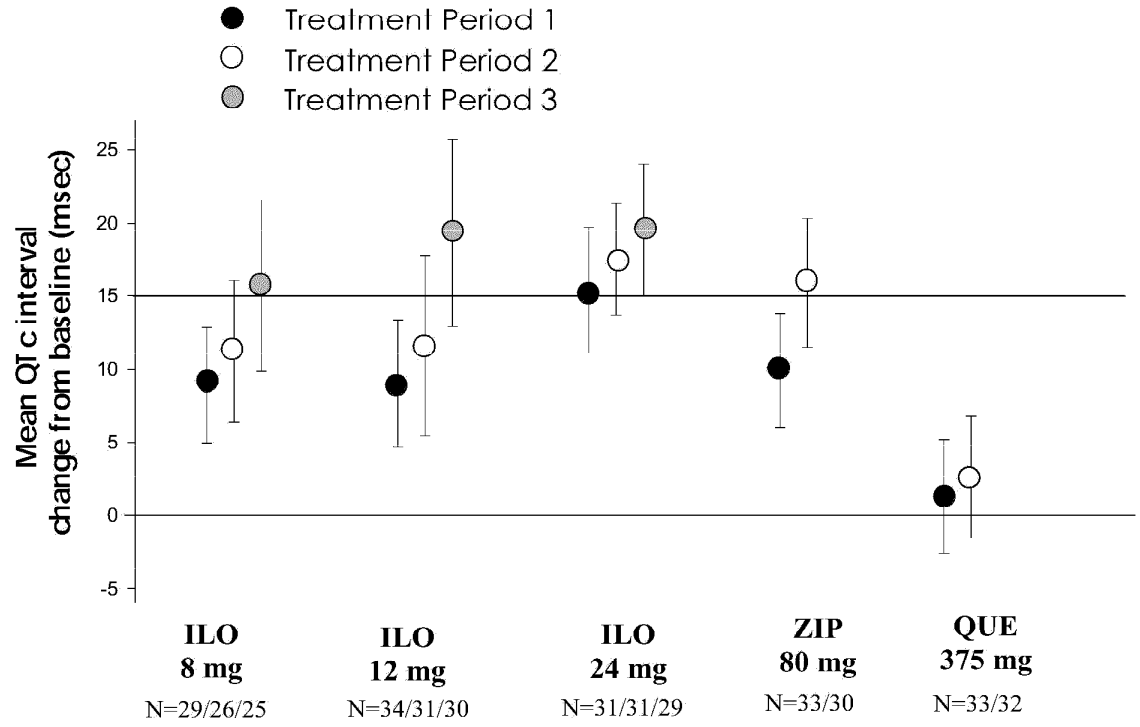
Table 9-2 Summary statistics of QTc change (95% CI) from baseline to steady state at T_{MAX}* during Treatment Periods 1, 2, and 3 (Secondary QTc population)

	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.
Treatment Period 1					
Baseline					
N	29	34	31	33	33
Mean ± SD (Fridericia)	385.5 ± 16.2	386.5 ± 17.1	379.0 ± 14.7	383.7 ± 13.4	383.2 ± 18.9
Mean ± SD (Baseline)	385.5 ± 16.2	386.5 ± 17.2	379.0 ± 14.7	383.8 ± 13.3	383.3 ± 19.0
Mean ± SD (FDA)	387.9 ± 15.9	389.5 ± 17.8	381.1 ± 14.4	386.5 ± 13.3	385.9 ± 19.3
Mean ± SD (Bazett)	396.8 ± 17.2	400.7 ± 22.1	388.8 ± 15.8	396.5 ± 16.2	395.6 ± 22.9
Change from baseline					
N	29	34	31	33	33
Mean ± SD (Fridericia)	8.9 ± 10.5	9.0 ± 12.5	15.4 ± 11.7	9.9 ± 11.0	1.3 ± 11.1
Mean ± SD (Baseline)	9.0 ± 10.5	9.0 ± 12.6	15.4 ± 11.6	9.9 ± 10.9	1.4 ± 11.1
Mean ± SD (FDA)	10.5 ± 10.7	10.4 ± 12.4	16.3 ± 11.8	10.9 ± 11.0	3.7 ± 11.3
Mean ± SD (Bazett)	16.0 ± 13.5	15.6 ± 13.9	19.3 ± 14.8	14.6 ± 12.7	12.6 ± 14.2
Treatment Period 2					
Baseline					
N	26	31	31	30	32
Mean ± SD (Fridericia)	387.3 ± 16.1	386.1 ± 17.7	379.0 ± 14.7	383.0 ± 13.2	382.8 ± 19.1
Mean ± SD (Baseline)	387.3 ± 16.1	386.1 ± 17.8	379.0 ± 14.7	383.1 ± 13.2	382.9 ± 19.1
Mean ± SD (FDA)	389.6 ± 15.8	389.1 ± 18.4	381.1 ± 14.4	385.7 ± 13.1	385.4 ± 19.5
Mean ± SD (Bazett)	398.5 ± 16.8	400.1 ± 22.8	388.8 ± 15.8	395.9 ± 16.0	395.2 ± 23.1
Change from baseline					
N	26	31	31	30	32
Mean ± SD (Fridericia)	11.2 ± 12.0	11.6 ± 16.8	17.5 ± 10.3	15.9 ± 11.8	2.6 ± 11.5
Mean ± SD (Baseline)	11.2 ± 11.9	11.5 ± 16.9	17.4 ± 10.2	16.0 ± 11.7	2.7 ± 11.5
Mean ± SD (FDA)	11.3 ± 11.9	10.7 ± 16.4	16.9 ± 10.0	17.0 ± 11.9	5.7 ± 11.9
Mean ± SD (Bazett)	11.4 ± 14.0	7.5 ± 17.8	15.0 ± 11.9	21.0 ± 13.9	17.2 ± 15.5
Treatment Period 3					
Baseline					
N	25	30	29	--	--
Mean ± SD (Fridericia)	387.5 ± 16.4	384.5 ± 15.6	379.6 ± 14.9	--	--
Mean ± SD (Baseline)	387.5 ± 16.4	384.5 ± 15.6	379.6 ± 14.9	--	--
Mean ± SD (FDA)	389.8 ± 16.1	387.5 ± 16.5	381.5 ± 14.7	--	--
Mean ± SD (Bazett)	398.5 ± 17.1	398.7 ± 21.8	388.7 ± 16.4	--	--
Change from baseline					
N	25	30	29		
Mean ± SD (Fridericia)	15.7 ± 14.1	19.3 ± 17.1	19.5 ± 11.9	--	--
Mean ± SD (Baseline)	15.7 ± 14.1	19.3 ± 17.1	19.4 ± 11.8	--	--
Mean ± SD (FDA)	15.8 ± 13.6	18.6 ± 16.7	19.0 ± 11.9	--	--
Mean ± SD (Bazett)	15.9 ± 14.5	15.8 ± 17.9	17.0 ± 13.9	--	--

N=number of patients; ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine
*T_{MAX}=estimated time of maximum concentration (ILO=2-4 hours post-dose; ZIP=5-7 hours post-dose; QUET=1-2.5 hours post-dose).

Source: Post-text Table 9.2.1-1

Figure 9-2 Mean QTc (Fridericia) Change (95%CI) from baseline to steady state at T_{MAX}* during Treatment Periods 1, 2, and 3 (Secondary QTc Population)



ILO=iloperidone; ZIP=ziprasidone; QUE=quetiapine
P1=Period 1, P2=Period 2, P3=Period 3
Note: * T_{MAX} = estimated time of maximum concentration (ILO=2-4 hours post-dose; ZIP=5-7 hours post-dose; QUET= 1-2.5 hours post-dose)
Source: Figure 9.2-1

9.2.2 Number and proportion of patients with increases from baseline in QTc at Tmax of ≥30 and 60 msec

The number and proportion of patients with QTcF increases of ≥ 30 msec from baseline to steady state at T_{max} during Treatment Period 1 was greatest in the iloperidone 24 mg q.d. [19/31 (61%)] group followed by the ziprasidone 80 mg b.i.d. [17/33 (52%], iloperidone 12 mg b.i.d. [15/34 (44%)], iloperidone 8 mg b.i.d. [9/29 (31%)], and quetiapine 375 mg b.i.d. [4/33 (12%)] groups, respectively (Table 9-3). Two patients in Treatment Period 1 experienced increases in QTcF of ≥ 60 msec from baseline to steady state at T_{max}. One patient was in the iloperidone 8 mg b.i.d. group and the other was in the iloperidone 24 mg q.d. group.

The number (%) of patients with QTcF increases of ≥ 30 msec from baseline to steady state at T_{max} during Treatment Period 2 was greatest in the iloperidone 24 mg q.d. [22/31 (71%)] group followed by the ziprasidone 80 mg b.i.d. [18/30 (60%], iloperidone 8 mg b.i.d. [14/26 (54%)], iloperidone 12 mg b.i.d. [15/31 (48%)], and quetiapine 375 mg b.i.d. [6/32 (19%)] groups, respectively (Table 9-3). In Treatment Period 2, the proportion of patients with QTcF increases at of ≥ 30 msec at Tmax in the iloperidone 12 mg b.i.d., iloperidone 24 mg q.d., and ziprasidone 80 mg b.i.d. was similar to Treatment Period 1. The proportion of patients with QTcF increases of ≥ 30 msec from baseline to steady state at Tmax in the iloperidone 8 mg b.i.d. and quetiapine 375 mg b.i.d. groups was higher in Treatment Period 2 compared with Treatment Period 1. Two patients in Treatment Period 2 experienced increases in QTcF of ≥ 60 msec from baseline to steady state at T_{max}. One patient was in the iloperidone 8 mg b.i.d. group and the other was in the iloperidone 24 mg q.d. group.

The number and proportion of patients with QTcF increases of ≥ 30 msec from baseline to steady state at T_{max} during Treatment Period 3 was greatest in the iloperidone 12 mg b.i.d. [21/30 (70%)] and iloperidone 24 mg q.d. [20/29 (69%)] groups followed by the iloperidone 8 mg b.i.d. [13/25 (52%)] group (Table 9-3).

In Treatment Period 3, the proportion of patients with QTcF increases of ≥ 30 msec at T_{max} in the iloperidone 8 mg b.i.d. and 24 mg q.d. treamtent groups was similar to that observed Treatment Period 2. The proportion of patients with QTcF increases of ≥ 30 msec at T_{max} in the iloperidone 12 mg b.i.d. was greater in Treatment Period 3 than in Treatment Period 2. Four patients in Treatment Period 3 experience increases in QTcF of ≥ 60 msec from baseline to steady state at T_{max}. One patient was in the iloperidone 8 mg b.i.d. group and the other 3 patients were in the iloperidone 12 mg b.i.d. group.

The number and proportion of patients with QTc increases of ≥ 30 and 60 msec from baseline to steady state at T_{max} using all 4 correction formulas is presented in Table 9-3. The number of patients (%) with QTc increases of ≥ 30 and 60 msec from baseline to SSD3 and from baseline to steady state (all evaluations) during Treatment Period 1 is summarized in Post-text Table 9.2.2-2 and Post-text Table 9.2.1-3 .

Table 9-3 Number (%) of patients with QTc increase from baseline to steady state at T_{MAX}* of ≥ 30 and 60 msec during Treatment Periods 1, 2, and 3 (Secondary QTc population)

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

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

Source: Post-text Table 9.2.1-3

9.2.3 Number of patients (%) with QTc values of ≥ 500 msec at Tmax

No patients experience QTc values (using any correction factor) of ≥ 500 msec during the conduct of this study (Post-text Listing 9.2-2).

9.2.4 Additional analysis

Mean changes in QTcF from Day 0 (9 ECGs were taken over the course of the day) to SSD3 (9 ECGs were also taken over the course of the day) were 6.5±12.1 msec for the iloperidone 8 mg b.i.d. group, 5.8±12.6 msec for the iloperidone 12 mg b.i.d. group, 9.6±11.7 msec for the iloperidone 24 mg q.d. group, 7.3±11.6 msec for the ziprasidone 80 mg b.i.d. group, and 1.8±10.7 msec for the quetiapine 375 mg b.i.d. group (Post-text Table 9.2.2-1). Mean QTcF changes from Day 0 to SSD3 during Treatment Period 1 were smaller than mean changes observed when QTcF measurements were taken at T_{max} in all treatment groups except for the quetiapine 375 mg b.i.d. group (Table 9.2).

Mean changes in QTcF from baseline (15 ECGs) to steady state during treatment period 1 (15 ECGs) were 7.7±9.7 msec for the iloperidone 8 mg b.i.d. group, 7.5±11.0 msec for the iloperidone 12 mg b.i.d. group, 11.9±9.6 msec for the iloperidone 24 mg q.d. group, 8.8±10.5 msec for the ziprasidone 80 mg b.i.d. group, and 1.0±9.3 msec for the quetiapine 375 mg b.i.d. group (Post-text Table 9.2.3-1).

Mean changes in QTcF from baseline to different times of the day on SSD3 during Treatment Period 1 were lowest in the evening which represented ECGs taken at approximate trough concentrations for compounds given b.i.d. The greatest change in QTcF values were observed at times corresponding to T_{max} of each compound (morning values for iloperidone and quetiapine and afternoon values for ziprasidone) with the exception of mean changes observed for the iloperidone 8 mg b.i.d. where the mean QTcF change in the afternoon (8.5±14.5) was numerically greater than the mean QTcF change observed in the morning (7.5±15.2) (Post-text Table 9.2.4-1). Both of these values (mean change in QTcF in the morning and afternoon) for the iloperidone 8 mg b.i.d. group were less than the mean change in QTcF from baseline to steady state at T_{max} during Treatment Period 1 (8.9±10.5) (Table 9.2).

9.3 Relationship of drug concentration to QTc interval analysis results

Complete pharmacokinetic/pharmacodynamic methodology and results are presented in a separate report Appendix 8. A summary of the results is presented below.

9.3.1 Drug concentration levels

Peak concentrations (parent and metabolites of the drugs) at steady-state day 1 (SSD1) and day 2 (SSD2) were examined and no significant difference was found between SSD1 and SSD2. The average of these two was then calculated and used in the subsequent analyses. 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 9-4. Patients who had no detectable concentrations or all concentrations below the limit of quantification in Period 1 were excluded. Patients with no detectable peak

concentrations in Periods 2 and 3 were also excluded from the summary. 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 qd 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 qd group and the highest in the iloperidone 8 mg b.i.d. For the primary active metabolite of iloperidone, P88, the corresponding increases in concentrations were comparable or slightly larger, i.e. 29-73% in Period 2, and 84-171% in Period 3. For iloperidone metabolite P95 (non-active), mean peak concentrations reduced to ~50% in Period 2 and to ~30% in Period 3, compared to the peak concentration levels without metabolic inhibition in Period 1. Mean peak concentration increases due to metabolic inhibitor ketoconazole were 24%, and 334% for ziprasidone, and quetiapine respectively.

Table 9-4 Average[a] peak concentrations and ratios of average peak concentrations in the presence and in the absence of metabolic inhibitors

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

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

9.3.2 Drug concentration vs QTc interval

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

change was the difference between the mean QTc during treatment and the mean QTc at baseline.

Mean QTc change from baseline at T_{max} in each treatment period was the dependent variable. The independent variables included the corresponding mean QTc at baseline, and concentrations (parent and metabolites) at their T_{max}. Concentrations were centered at the sample mean in each treatment period, and scaled by ~ 1/2 standard deviation, i.e. 10 ng/mL for iloperidone and metabolites, 50 ng/mL for ziprasidone, and 500 ng/mL for quetiapine. Baseline mean QTc was centered at 385 msec and scaled by 10 msec. 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 msec. 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 msec 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 9-5. 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 msec increase in baseline QTc resulted in a 2-4 msec 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 ($p \geq 0.3861$).

Table 9-5 Modeling the effect of drug and metabolites concentrations on the mean QTc change at Tmax

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

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

10 Safety results

The safety analysis included all patients who received at least one dose of study medication and from whom at least one safety measurement was obtained post-baseline.

10.1 Overall experience of adverse events (AEs)

The number of patients with at least one AE was higher in the iloperidone 12 mg b.i.d. group (97%) than in the iloperidone 8 mg b.i.d. (88%), iloperidone 24 mg q.d. (91%), ziprasidone (91%), and quetiapine (86%) groups. The most frequently affected organ system classes were the nervous system, gastrointestinal system and psychiatric disorders (Table 10-1). The Total number of patients in Table 10-1 include five patients from the risperidone arm that was removed from the study, as per Amendment 2 (see Section 4.1).

Table 10-1 Number (%) of patients with AEs, overall and by body system (Safety population)

	ILO 8 mg b.i.d.	ILO 12 mg b.i.d.	ILO 24mg q.d.	ZIP 80 mg b.i.d.	QUET 375 mg b.i.d.	Total
	N = 34	N = 37	N = 35	N = 34	N = 35	N=175
	n (%)	n (%)	n (%)	n (%)	n (%)	N (%)
Total No. With One Or More AEs	30 (88)	36 (97)	32 (91)	31 (91)	30 (86)	164 (91)
Nervous System Disorders	17 (50)	23 (62)	21 (60)	20 (59)	21 (60)	106 (59%)
Gastrointestinal Disorders	13 (38)	22 (59)	20 (57)	14 (41)	17 (49)	88 (49%)
Psychiatric Disorders	10 (29)	14 (38)	12 (34)	10 (29)	8 (23)	58 (32%)
Respiratory, Thoracic and Mediastinal Disorders	6 (18)	12 (32)	11 (31)	8 (24)	5 (14)	45 (25%)
General Disorders And Administration Site Conditions	5 (15)	6 (16)	11 (31)	13 (38)	6 (17)	42 (23%)
Musculoskeletal And Connective Tissue Disorders	4 (12)	9 (24)	4 (11)	6 (18)	6 (17)	29 (16%)
Infections And Infestations	4 (12)	6 (16)	8 (23)	3 (9)	6 (17)	29 (16%)
Skin And subcutaneous Tissue Disorders	8 (24)	8 (22)	4 (11)	1 (3)	0 (0)	21 (12%)
Cardiac Disorders	2 (6)	8 (22)	2 (6)	1 (3)	2 (6)	15 (8%)
Eye Disorders	0 (0)	3 (8)	4 (11)	2 (6)	0 (0)	9 (5%)
Reproductive System And Breast Disorders	3 (9)	2 (5)	3 (9)	1 (3)	0 (0)	9 (5%)
Ear And Labyrinth Disorders	2 (6)	1 (3)	3 (9)	1 (3)	1 (3)	9 (5%)
Metabolism And Nutrition Disorders	0 (0)	1 (3)	2 (6)	2 (6)	2 (6)	7 (4%)
Renal And Urinary disorders	1 (3)	2 (5)	2 (6)	1 (3)	1 (3)	7 (4%)
Vascular Disorders	1 (3)	2 (5)	1 (3)	2 (6)	1 (3)	7 (4%)
Injury, Poisoning	0 (0)	2 (5)	0 (0)	2 (6)	2 (6)	6 (3%)
Immune System Disorders	0 (0)	4 (11)	0 (0)	0 (0)	0 (0)	4 (2%)
Investigations	0 (0)	1 (3)	0 (0)	2 (6)	1 (3)	4 (2%)

	ILO 8 mg b.i.d.	ILO 12 mg b.i.d.	ILO 24mg q.d.	ZIP 80 mg b.i.d.	QUET 375 mg b.i.d.	Total
	N = 34	N = 37	N = 35	N = 34	N = 35	N=175
Blood And Lymphatic System Disorders	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (1%)

ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine; Source: Post-text table 10.1.1-1

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 (Table 10-2).

Table 10-2 Number (%) of patients with most common (≥10%) AEs, by body system and preferred term (Safety population)

	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 = 34	N = 37	N = 35	N = 34	N = 35
	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. with one or more AEs	30 (88)	36 (97)	32 (91)	31 (91)	30 (86)
Body system					
Preferred term					
Cardiac Disorders	2 (6)	8 (22)	2 (6)	1 (3)	2 (6)
Tachycardia NOS	1 (3)	7 (19)	2 (6)	1 (3)	1 (3)
Gastrointestinal Disorders	13 (38)	22 (59)	20 (57)	14 (41)	17 (49)
Dyspepsia	2 (6)	9 (24)	7 (20)	6 (18)	4 (11)
Dry Mouth	4 (12)	5 (14)	5 (14)	2 (6)	8 (23)
Constipation	0 (0)	7 (19)	7 (20)	4 (12)	4 (11)
Nausea	1 (3)	2 (5)	2 (6)	6 (18)	3 (9)
Diarrhea NOS	1 (3)	6 (16)	1 (3)	0 (0)	2 (6)
General Disorders And Administration Site Conditions	5 (15)	6 (16)	11 (31)	13 (38)	6 (17)
Fatigue	4 (12)	4 (11)	5 (14)	6 (18)	4 (11)
Nervous System Disorders	17 (50)	23 (62)	21 (60)	20 (59)	21 (60)
Headache NOS	10 (29)	8 (22)	9 (26)	7 (21)	3 (9)
Sedation	1 (3)	5 (14)	4 (11)	4 (12)	11 (31)
Somnolence	4 (12)	5 (14)	4 (11)	5 (15)	6 (17)
Dizziness	3 (9)	7 (19)	3 (9)	3 (9)	5 (14)
Extrapyramidal Disorder	2 (6)	6 (16)	1 (3)	6 (18)	3 (9)
Akathisia	2 (6)	4 (11)	2 (6)	4 (12)	1 (3)
Psychiatric Disorders	10 (29)	14 (38)	12 (34)	10 (29)	8 (23)
Anxiety	6 (18)	10 (27)	9 (26)	5 (15)	2 (6)
Insomnia	3 (9)	7 (19)	8 (23)	5 (15)	2 (6)
Respiratory, Thoracic And Mediastinal Disorders	6 (18)	12 (32)	11 (31)	8 (24)	5 (14)
Nasal Congestion	4 (12)	5 (14)	5 (14)	3 (9)	1 (3)
Pharyngitis	1 (3)	4 (11)	1 (3)	3 (9)	3 (9)
Cough	2 (6)	3 (8)	4 (11)	0 (0)	0 (0)

ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine; NOS=not otherwise specified

Source: Post-text table 10.1.1-1

Of these adverse events, headache, anxiety, dyspepsia, insomnia, constipation, dizziness, tachycardia, diarrhea, nasal congestion, and cough occurred at a higher rate for iloperidone-treated patients than both ziprasidone and quetiapine. The incidence of headache was higher in all iloperidone-treatment groups (29%, 22%, and 26% for ILO 8 mg b.i.d, ILO 12 mg b.i.d. and ILO 24 mg q.d., respectively) and in the ziprasidone-treatment group (21%) than the incidence in the quetiapine group (9%). Anxiety occurred at the higher rate in all the iloperidone-treatment groups (ILO 8 mg b.i.d.=18%, ILO 12 mg b.i.d.=27%, ILO 24 mg q.d.=26%) in comparison to the quetiapine (6%) group. The incidence of insomnia was higher in patients treated with the higher iloperidone dosage regimens (ILO 12 mg b.i.d.=19%, ILO 24 mg q.d.=23%) than the incidence in the quetiapine group (6%).

Constipation was reported more frequently in the higher iloperidone dosage groups (ILO 12 mg b.i.d.=19%, ILO 24 mg q.d.=20%) in comparison to ziprasidone (12%) or quetiapine (11%) treatment groups. Dizziness was reported more frequently in the iloperidone 12 mg b.i.d. (19%) group than in the ziprasidone (9%) group but was reported at a similar frequency as the quetiapine group (14%). The incidence of tachycardia was higher in the iloperidone 12 mg b.i.d. group (19%) than the incidence in the ziprasidone (3%), or quetiapine (3%) groups. Diarrhea occurred more frequently in the iloperidone 12 mg b.i.d. group (16%) than in the quetiapine (6%) or ziprasidone (0%) groups. The incidence of nasal congestion was higher in the iloperidone (ILO 8 mg b.i.d.=12%, ILO 12 mg b.i.d.=14%, ILO 24 mg q.d.=14%) treatment groups than the incidence in the quetiapine group (3%). Cough occurred more frequently in the iloperidone 24 mg q.d. treatment (11%) group than in the ziprasidone (0%) or quetiapine treatment (0%) groups.

Adverse events that occurred more frequently in the higher iloperidone b.i.d. dosage regimen (iloperidone 12 mg b.i.d.) than the lower b.i.d. dosage regimen (iloperidone 8 mg b.i.d.) were anxiety (27 % vs 18%), dyspepsia (24% vs 6%), constipation (19% vs 0%), dizziness (19% vs 9%), insomnia (19% vs 9%), tachycardia (19% vs 3%), diarrhea (16% vs 3%), EPS (16% vs 6%), sedation (14% vs 3%), akathisia (11% vs 6%), and pharyngitis (11% vs 3%). Of these AEs, dyspepsia, constipation, insomnia, and sedation also occurred at a higher rate in the iloperidone 24 mg q.d. group than the iloperidone 8 mg b.i.d. group. No commonly occurring AEs occurred at a substantially higher rate in the iloperidone 24 mg q.d. group than the iloperidone 12 mg b.i.d. group.

Commonly occurring AEs in the ziprasidone group included headache, EPS, dyspepsia, fatigue, nausea, anxiety, insomnia, somnolence, akathisia, constipation, and sedation (Table 10-2).

The most common treatment-emergent AEs that occurred at a higher rate for ziprasidone-treated patients than both quetiapine and iloperidone were headache, EPS, nausea, fatigue, and akathisia. The incidence of nausea was higher in the ziprasidone (18%) group than the quetiapine (9%), iloperidone 24 mg q.d. (6%), iloperidone 12 mg b.i.d. (5%), and iloperidone 8 mg b.i.d. (3%) groups. The incidence of EPS was higher in the ziprasidone (18%) group than in the iloperidone 8 mg b.i.d. (6%), iloperidone 24 mg q.d. (3%), and quetiapine (9%) groups but was similar to then incidence in the iloperidone 12 mg b.i.d. (16%). The incidence of akathisia was higher in the ziprasidone (12%) groups than in the iloperidone 8 mg b.i.d. (6%), iloperidone 24 mg q.d. (6%), or quetiapine (3%) groups but was similar to the iloperidone 12 mg b.i.d. (11%) group.

Commonly occurring AEs in the quetiapine group included sedation, dry mouth, dizziness, constipation, dyspepsia, somnolence, and fatigue (Table 10-2).

The most common treatment-emergent AEs that occurred at a higher rate for quetiapine-treated patients than both ziprasidone and iloperidone were dry mouth and sedation. The incidence of dry mouth was higher in the quetiapine group (23%) than the incidence in the iloperidone 12 mg b.i.d. (14%), iloperidone 24 mg q.d. (14%), iloperidone 8 mg b.i.d. (12%), or the ziprasidone group (6%). The incidence of sedation was higher in the quetiapine (31%) group than the incidence in the iloperidone 12 mg b.i.d. (14%), ziprasidone (12%), iloperidone 24 mg q.d. (11%), or the iloperidone 8 mg b.i.d. groups (3%).

Overall AEs by severity

Most AEs were reported as mild or moderate; very few patients experienced AEs rated as severe (3 patients treated with iloperidone 8 mg b.i.d, 3 patients treated with ziprasidone 80 mg b.i.d., and 1 patient treated with quetiapine 375 mg b.i.d.). The AEs reported as severe in the iloperidone 8 mg b.i.d. group were supraventricular tachycardia (also reported as a SAE), EPS, and confusional state. Those reported as severe in the ziprasidone group were decreased appetite, headache, and agitation. Nausea and dizziness were the only AEs reported as severe in the quetiapine group (Post-text Table 10.1.1-3).

Overall AEs by relationship to study medication

Treatment emergent AEs that were suspected by the investigator were highest in the ziprasidone group (68%) and similar for the iloperidone 12 mg b.i.d. (59%), iloperidone 24 mg q.d. (57%), and quetiapine (60%). The lowest incidence was observed in the iloperidone 8 mg b.i.d. (50%) (Post-text Table 10.1.1-4). Those events with a suspected relationship to study drug and of higher incidence were tachycardia and akathisia in the iloperidone 12 mg b.i.d. treatment group (19% and 11%, respectively), dizziness and somnolence in the iloperidone 12 mg b.i.d. (14% and 14%, respectively) and quetiapine (14% and 17%, respectively) treatment groups, EPS in the iloperidone 12 mg b.i.d. (14%) and ziprasidone (15%) treatment groups, and sedation (26%) and dry mouth (17%) in the quetiapine group (Post-text Table 10.1.1-4).

Overall AEs by Treatment Period

The majority of the AE that were reported in this study occurred during Treatment Period 1. Common AEs overall were similar to common AEs reported during the Treatment Period 1. During Treatment Periods 2 and 3, there were no AEs that occurred at a rate of > 10% in any treatment group (Post-text Table 10.1.1-2).

10.2 Deaths, other serious and other significant adverse events

No deaths were reported during this trial. Other serious or significant events are summarized in Table 10-3 and discussed in Sections 10.2.1 through 10.2.3.

Table 10-3 Number (%) of patients who died or had other serious or clinically significant[a] AEs by treatment (Safety population)

	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 = 34	N = 37	N = 35	N = 34	N = 35
Total no. of patients	n (%)	n (%)	n (%)	n (%)	n (%)
Serious or significant events					
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs	1 (3)	0 (0)	1 (3)	0 (0)	1 (3)
Any other significant AE resulting in					
Discontinued due to AEs	3 (9)	2 (5)	1 (3)	2 (6)	1 (3)
Concomitant medication taken	26 (76)	35 (95)	28 (80)	24 (71)	16 (46)

N=number of patients; ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine
[a] Other significant AEs include events that were not necessarily serious but required intervention (i.e., resulted in discontinuation, dose adjustment/interruption, or concomitant medication/significant non-drug therapy) or were considered clinically important by the Sponsor.
Note: One patient experienced a SAE before randomization, and one patient experienced a SAE after study medication was discontinued
Source: Post-text Table 10.1.2-1, Post-text Table 10.1.2-2, Post-text Table 10.1.2-3, Post-text Table 10.1.1-5, Post-text Listing 10.2-1, Post-text Listing 10.2-4

10.2.1 Serious adverse events (SAEs)

Three patients experienced a serious adverse event (SAEs) during treatment with study medication (Post-text Table 10.1.2-2) and these events are listed in Table 10-4. Additionally, one patient (0516_0001) experienced a SAE (altered mental status and brief psychotic reaction) before randomization, and one patient (0502_0066) experienced a SAE (pain in extremities and shortness of breath) after study medication (iloperidone 8 mg b.i.d.) was discontinued. These two cases were reported to Novartis Department of Safety and Epidemiology but were not recorded in the Case Record Form (CRF) because these events did not occur during study drug administration and therefore are not included in Table 10-4 or Post-text listing 10.2-2. Safety narratives for all patients who experienced an SAE are presented in Post-text Supplement 2.

Table 10-4 Patients with serious adverse events (SAEs) (Safety population)

Treatment group	Patient No.	Age/Sex/Race	Preferred Term	Study Day
ILO 8 mg b.i.d.	0522_00006	36/M/OT	Supraventricular tachycardia	8
ILO 24 mg q.d.	0502_00024	47/F/CA	Diabetes mellitus inadequate control	32
QUET 375 mg b.i.d.	0501_00031	41/F/OT	Psychosis aggravated	5

ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine
Source: Post-text Listing 10.2-2

10.2.2 Other significant adverse events

Other significant AEs include events that were not serious but required intervention (i.e., resulted in discontinuation, dose adjustment/interruption, or concomitant medication/significant nondrug therapy) or were considered clinically important by the Sponsor.

AEs resulting in discontinuation

Nine patients experienced AEs that lead to premature discontinuation (Table 10-5). The number of events was similar across treatment groups; iloperidone 8 mg b.i.d.=3(9%), iloperidone 12 mg b.i.d.=2(5%), iloperidone 24 mg q.d.=1(3%), ziprasidone=2(6%), quetiapine=1(3%; Post-text Table 10.1.2-3). Safety narratives for these patients are presented in Post-text supplement 2.

Table 10-5 Patients with adverse events leading to discontinuation (Safety population)

Treatment group	Patient No.	Age/Sex/ Race	Preferred Term	Study Day
ILO 8 mg b.i.d.	0516_00008	47/M/CA	Confusional state	22
	0518_00010	48/M/CA	Rash erythematous	4-8
	0522_00006	36/M/OT	Supraventricular tachycardia	8
ILO 12 mg b.i.d.	0502_00066	29/M/BL	Sleep apnoea syndrome	15
	0516_00007	49/M/CA	Sinus bradycardia	30
ILO 24 mg q.d.	0513_00001	43/M/CA	Tachycardia NOS	5
ZIP 80 mg b.i.d.	0502_00017	45/M/BL	Headache NOS	6-9
	0522_00007	44/M/CA	Psychosis aggravated	7
QUET 375 mg b.i.d.	0501_00031	41/F/OT	Psychosis aggravated	5

ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine; NOS=not otherwise specified
Source: Post-text Listing 10.2-3

AEs resulting in dosage adjustment or temporary interruption of one or more scheduled doses of study medication

Only 3 patients experienced AEs that resulted in dose adjustment or temporary interruption. Two patients were in the iloperidone 12 mg b.i.d. treatment group (psychosis aggravated, contusion) and one patient was in the iloperidone 24 mg qd group (tachycardia) (Post-text Listing 10.2-4).

These dose interruptions/adjustments occurred during dose escalation and lasted 1-3 days. As these 3 patients were randomized to iloperidone, each received their target dose for 5 days (as per protocol) before steady state assessments were conducted.

AEs resulting in concomitant medication or non-drug therapy

Adverse events that have resulted in concomitant medication administration was highest for the iloperidone 12 mg b.i.d. group (95%), similar for iloperidone 8 mg b.i.d. (76%), iloperidone 24 mg q.d. (80%), and ziprasidone (71%), and lowest in the quetiapine group (46%) (Post-text Table 10.1.1-5). A listing of patients that experience adverse events resulting in administration of concomitant medication are presented by treatment in Post-text Listing 10.2-5.

Overdose

Cases of overdose were considered clinically important by the Sponsor if they were symptomatic or required therapy. No such cases of overdose occurred during this study (Post-text Table 10.1.1-1).

Pregnancy

No pregnancies occurred during this study (Post-text Listing 10.2.3-1).

10.2.3 Evaluation of deaths and other serious or significant adverse events

No deaths and a small number of SAEs occurred in patients receiving active treatment. No dose dependent or clinically important trends were seen among the iloperidone groups.

10.3 Laboratory values

Laboratory variables were analyzed according to the statistical methodology outlined in Section 6. Results from the analyses of central tendency (summary statistics), frequency of abnormalities based on the extended normal range (±15% [±10% for electrolytes] of the normal range), and frequency of abnormalities based on clinically notable criteria (also known as "markedly abnormal" criteria; Post-text Supplement 1) were summarized separately in post-text tables. For each of these analyses, results were presented separately for hematology, chemistry, and urinalysis.

10.3.1 Summary statistics

The mean changes from baseline in laboratory values were similar in all treatment groups, with the exception of changes observed in blood glucose and creatine kinase. Although mean changes in blood glucose observed in the iloperidone 12 mg b.i.d. (22.6±58.7 mg/dL) and iloperidone 24 mg q.d. (47.5±193.8 mg/dL) groups were greater in comparison to ziprasidone (6.7±30.7 mg/dL) and quetiapine (14.9±34.1 mg/dL), these values were influenced by outliers as reflected in larger standard deviations associated with these changes. In particular, the mean change observed in the iloperidone 24 mg q.d. group was influenced by a 1061 mg/dL change from baseline observed for patient 0502_00024 (Post-text Listing 10.3.1-2). This incident was reported as an SAE and a safety narrative is presented in Post-text supplement 2. Additionally, the median values for the iloperidone 24 mg q.d. (1.0 mg/dL) group was smaller than the median values observed in the other treatment groups (iloperidone 8 mg b.i.d.=7.0 mg/dL, iloperidone 12 mg b.i.d.=10 mg/dL, ziprasidone=1.5 mg/dL, quetiapine=9.0 mg/dL).

Similarly, the mean change in creatine kinase was greater in the iloperidone 8 mg b.i.d. (139.4±456.1 U/L) group in comparison to the ziprasidone (45.4±119 U/L) or quetiapine (13.7±103.8 U/L) groups; however, this value was influence by outliers as reflected in the larger standard deviation associated with this change. In particular, the mean change in the iloperidone 8 mg b.i.d. group was influenced by a change from baseline of 2472 U/L observed for patient 0502_00043. Furthermore, the median value for the iloperidone 8 mg b.i.d. (18.0 U/L) was smaller than the median values observed for iloperidone 12 mg b.i.d. (34.0 U/L), iloperidone 24 mg q.d. (27.0 U/L), ziprasidone (21.5 U/L), and the same as the median value observed for quetiapine (18.0 U/L).

In general, no dose-dependent effects on changes in laboratory values from baseline were observed among the iloperidone groups. (Post-text Tables 10.3.1-1, 10.3.1-2 , and 10.3.1-3 for hematology, chemistry, and urinalysis results, respectively).

10.3.2 Frequency of abnormalities based on extended normal range

Categorical analysis

The overall incidence of laboratory values outside the extended normal range (See Section 6.1.6 for definition) was similar across the treatments with the exception of SGPT, which a higher frequency was observed in the ziprasidone (22%) and quetiapine (18%) groups than the iloperidone groups (iloperidone 8 mg b.i.d.=12%, iloperidone 12 mg b.i.d.=3%, iloperidone 24 mg q.d.=6%), SGOT, which a higher frequency was observed in the quetiapine (12%) group than the iloperidone (iloperidone 8 mg b.i.d.=6%, iloperidone 12 mg b.i.d.=6%, iloperidone 24 mg q.d.=6%) groups or the ziprasidone (3%) group, and triglycerides, which a higher frequency was observed in the quetiapine (24%) group than ziprasidone (9%) or iloperidone (iloperidone 8 mg b.i.d.=3%, iloperidone 12 mg b.i.d.=5%, iloperidone 24 mg q.d.=3%) group (source = Post-text Tables 10.3.2-1 and 10.3.2-2 for hematology and chemistry results, respectively).

Of note, the frequency of abnormalities outside of the extended normal range for blood glucose was similar or less than ziprasidone (13%) and quetiapine (18%) for the iloperidone (iloperidone 8 mg b.i.d.=9%, iloperidone 12 mg b.i.d.=14%, iloperidone 24 mg q.d.=15%) groups (Table 10-6). The frequency of abnormalities outside the extended normal range for creatine kinase was similar for the iloperidone (iloperidone 8 mg b.i.d.=27%, iloperidone 12 mg b.i.d.=31%, iloperidone 24 mg q.d.=21%) groups and the ziprasidone (28%) group but higher than the frequency observed in the quetiapine (6%) group.

Table 10-6 Number (%) of patients with laboratory values outside the extended normal range (Safety population)

Treatment group		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.	
Abnormal values*		N	n (%)	N	n (%)	N	N (%)	N	N (%)	N	n (%)
ABS basophils	High	32	0 (0)	36	0 (0)	32	0 (0)	32	1 (3)	32	0 (0)
ABS neutrophils	High	32	1 (3)	36	0 (0)	32	1 (3)	32	3 (9)	32	1 (3)
	Low	32	1 (3)	36	0 (0)	32	0 (0)	32	2 (6)	32	0 (0)
Eosinophils %	High	32	1 (3)	36	0 (0)	32	0 (0)	32	1 (3)	32	0 (0)
Lymphocytes %	Low	32	0 (0)	36	1 (3)	32	0 (0)	32	0 (0)	32	0 (0)
Monocytes %	High	32	0 (0)	36	0 (0)	32	0 (0)	32	0 (0)	32	1 (3)
Neutrophils %	Low	32	0 (0)	36	0 (0)	32	0 (0)	32	1 (3)	32	0 (0)
Platelets	High	32	0 (0)	36	0 (0)	29	1 (3)	32	0 (0)	32	1 (3)
	Low	32	1 (3)	36	0 (0)	29	0 (0)	32	0 (0)	32	0 (0)
WBC	High	32	1 (3)	36	0 (0)	32	0 (0)	32	0 (0)	32	0 (0)
	Low	32	0 (0)	36	0 (0)	32	0 (0)	32	1 (3)	32	0 (0)
Alk phos	High	33	0 (0)	37	1 (3)	33	3 (9)	32	1 (3)	33	2 (6)
Cholesterol	High	33	0 (0)	37	1 (3)	33	0 (0)	32	2 (6)	33	0 (0)
	Low	33	3 (9)	37	2 (5)	33	1 (3)	32	1 (3)	33	0 (0)
CK	High	33	9 (27)	36	11 (31)	33	7 (21)	32	9 (28)	33	2 (6)
Creatinine	High	33	0 (0)	37	0 (0)	33	0 (0)	32	0 (0)	33	3 (9)
Glucose	High	33	3 (9)	36	5 (14)	33	5 (15)	32	4 (13)	33	6 (18)
	Low	33	0 (0)	36	0 (0)	33	1 (3)	32	0 (0)	33	1 (3)
LDH	High	33	1 (3)	36	1 (3)	33	0 (0)	30	1 (3)	33	0 (0)
Potassium	High	33	0 (0)	37	1 (3)	32	0 (0)	32	0 (0)	33	0 (0)
SGOT	High	33	2 (6)	36	2 (6)	33	2 (6)	32	1 (3)	33	4 (12)
SGPT	High	33	4 (12)	36	1 (3)	33	2 (6)	32	7 (22)	33	6 (18)
Triglycerides	High	33	1 (3)	37	2 (5)	33	1 (3)	32	3 (9)	33	8 (24)
Uric acid	High	33	4 (12)	37	4 (11)	33	0 (0)	32	2 (6)	33	3 (9)

ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine; ABS=absolute; alk phos=alkaline phosphatase; CK=creatine kinase

Source: Post-text Tables 10.3.2-1, 10.3.2-2

Transition analysis

A transition analysis of laboratory data was performed in order to investigate changes from baseline values to worst post-baseline values. Shift tables were constructed based on categories (low, normal, and high) of baseline and worst post-baseline values for routine laboratory tests (Post-text Tables 10.3.3-1 and 10.3.3-2 for hematology and chemistry results, respectively).

In general, changes from normal baseline values to the worst post-baseline values were similar across treatment groups, with the exception of creatine kinase, blood glucose, uric acid, SGOT, SGPT, and triglycerides. A greater percentage of patients in the iloperidone 12 mg b.i.d. (31%) group experienced changes from a normal baseline creatine kinase value to a higher value outside of the normal range than patients in the ziprasidone (9%) or quetiapine (3%) groups. Frequency of changes from a normal baseline blood glucose value to a higher value outside of the normal range were similar in the iloperidone 12 mg b.i.d (14%),

iloperidone 24 mg q.d. (15%), and quetiapine (12%) groups but were higher than the frequency of abnormal values in the iloperidone 8 mg b.i.d. (6%) and ziprasidone (9%) groups. A greater percentage of patients in the iloperidone 8 mg b.i.d. (12%), iloperidone 12 mg b.i.d. (11%), and quetiapine (9%) groups experienced a change from a normal baseline uric acid value to a higher post-baseline value outside the normal extended range than patients in the iloperidone 24 mg q.d. (0%) and ziprasidone (3%) groups.

A greater percentage of patients in the quetiapine group experienced a change from normal baseline SGOT (12%) and triglyceride (21%) values to a higher post-baseline values outside the normal extended range than patients in the iloperidone 8 mg b.i.d. (6%, 0%, respectively), iloperidone 12 mg b.i.d. (6%, 0%, respectively), and iloperidone 24 mg q.d. (6%, 0%, respectively) and ziprasidone (3%, 9%, respectively) groups. A greater percentage of patients in the ziprasidone (19%) group experienced a change from a normal baseline SGPT value to a higher post-baseline value outside the normal extended range than patients in the iloperidone 8 mg b.i.d. (12%), iloperidone 12 mg b.i.d. (3%), iloperidone 24 mg q.d. (6%), and quetiapine (12%) groups.

10.3.3 Frequency of abnormalities based on clinically notable criteria (also known as "markedly abnormal" criteria)

The incidence of clinically notable laboratory values was similar among the five treatments. In general, no dose-dependent effects were observed among the iloperidone groups (Post-text Tables 10.3.4-1, 10.3.4-2 and 10.3.4-3 for hematology, chemistry, and urinalysis results, respectively).

For hematology, the clinically notable abnormalities were reported for elevated eosinophils, decreased hematocrit, decreased hemoglobin, and decreased total WBC. No greater than 2 patients in any treatment group experienced any one of these abnormalities.

For biochemistry, clinically notable values were reported only for high uric acid (1 patient in the iloperidone 8 mg b.i.d. treatment group and 1 patient in the ziprasidone treatment group).

For urinalysis, clinically notable abnormalities were reported for high urine glucose [ILO 12 mg b.i.d.=2(6%), ILO 24 mg q.d.=4(12%), ZIP=1(3%)] and high urine protein [ILO 12 mg b.i.d.=1(3%), ZIP=1(3%)]

Further information concerning patients with clinically notable values is presented for hematology in Post-text Listing 10.3-1, for chemistry in Post-text Listing 10.3-2 and for urinalysis in Post-text Listing 10.3-3. Criteria for clinically notable laboratory abnormalities are presented in Post-Text Supplement 1.

10.4 Vital signs

Vital signs variables were analyzed according to the statistical methodology outlined in Section 6. Results for analyses of central tendency (summary statistics) and frequency of abnormalities based on clinically notable criteria (also known as "markedly abnormal" criteria; Post-text Supplement 1) are summarized separately in post-text tables. For each, results are presented separately for pulse/blood pressure and for weight/body temperature.

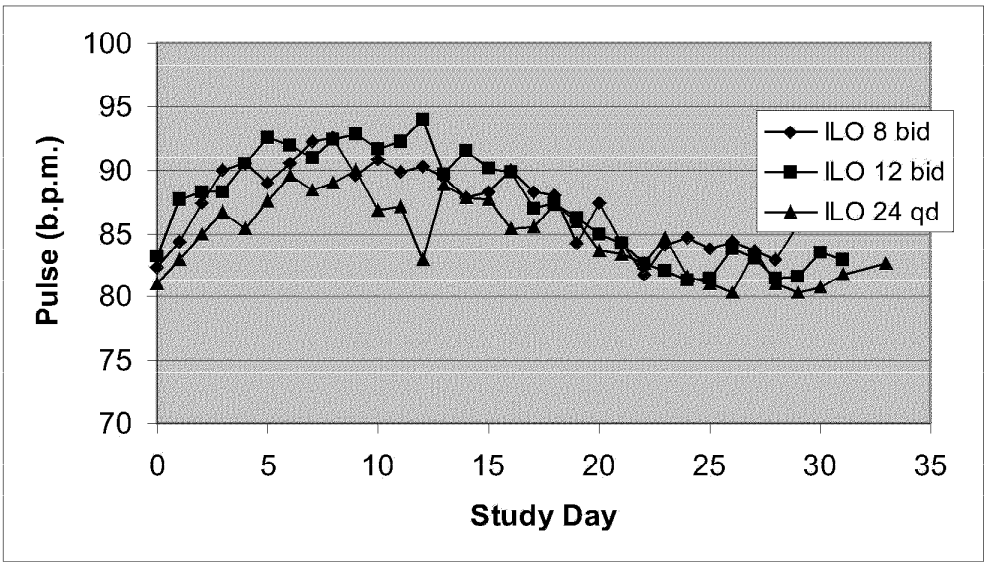
10.4.1 Summary statistics

Pulse and blood pressure

Vital signs were recorded twice daily for each patient after the patient remained in a seated position for 3 minutes. The value for each day represents the mean of the two values (a.m. and p.m.) for each patient. The value at baseline (Day 0) represents the average of vital signs collected over 3 days (-2, -1, 0).

As seen in previous iloperidone studies, mean heart rate increased by approximately 10 b.p.m. for all iloperidone treatment groups during the first week and returned to near baseline values by week 3 (Figure 10-1). A similar increase was also observed in the quetiapine group (Post-text Figure 10.4-1). The mean heart rate increase observed in the ziprasidone group during the first week was less (~5 b.p.m.) than the mean increase observed in the iloperidone and quetiapine treatment groups.

Figure 10-1 Pulse (3-minute sitting) over time by treatment \ Safety population

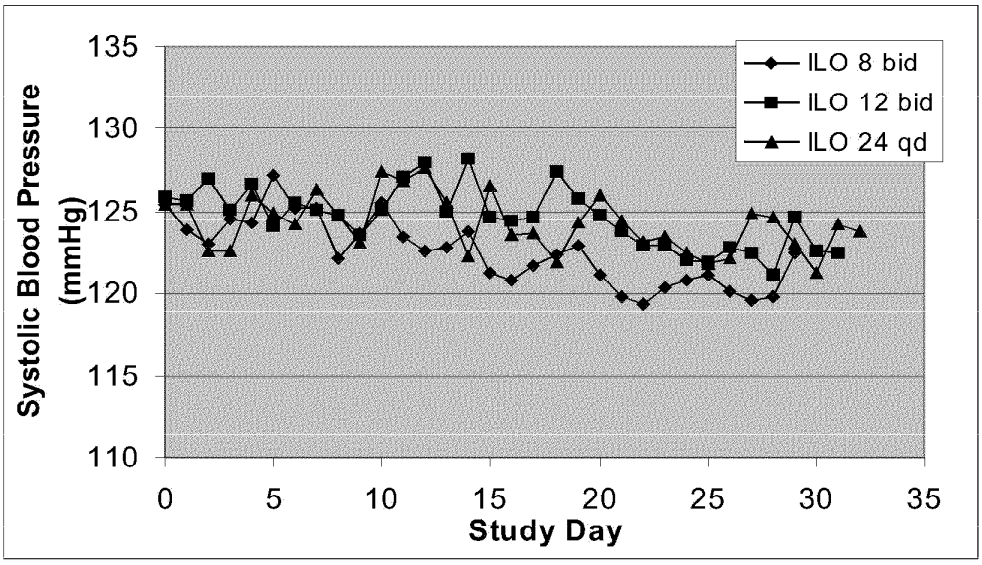


Source: Post-text Figure 10.4-1, Post-text Table 10.4.1-1

Mean systolic blood pressure decreased, but did not change substantially in any iloperidone treatment group over the course of this study (Figure 10-2 .

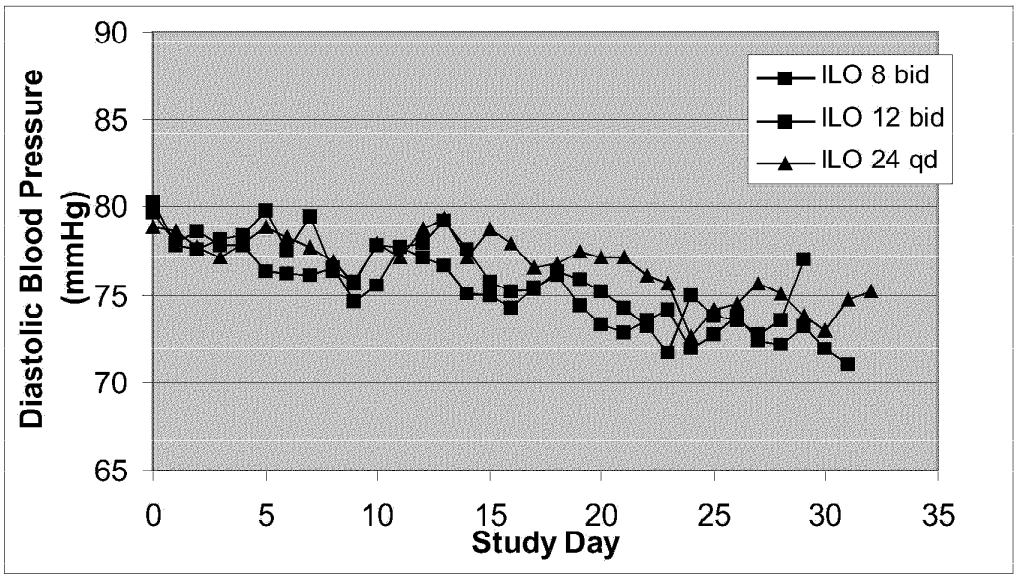
Mean diastolic blood pressure decreased gradually in all iloperidone treatment groups over the course of the study (Figure 10.3). The mean change from baseline to endpoint was –2.0, –7.5, –4.0 for ILO 8, 12, 24, respectively (Post-text Table 10.4.1-1).

Figure 10-2 Mean systolic blood pressure over time by treatment \ Safety population



Source: Post-text Figure 10.4-1, Post-text Table 10.4.1-1

Figure 10-3 Mean diastolic blood pressure over time by treatment \ Safety population



Source: Post-text Figure 10.4-1, Post-text Table 10.4.1-1

Weight and body temperature

Summary statistics at endpoint by treatment are presented for weight and body temperature in Post-text Table 10.4.2-1. The mean change in weight from baseline to endpoint was similar in the iloperidone 8 mg b.i.d. (3.2 kg), iloperidone 24 mg q.d. (3.3 kg), and quetiapine (2.6 kg) groups. The mean change in weight from baseline to endpoint was lower in the iloperidone 12 mg b.i.d. (1.2 kg) and ziprasidone groups (0.8 kg). Since the duration of treatment between iloperidone and the comparators was not the same direct comparison from baseline to final visit for weight may not be accurate.

10.4.2 Frequency of abnormalities based on clinically notable criteria (also known as "markedly abnormal" criteria)

Sitting 3-minute blood pressure and pulse

During treatment period 1, the number of patients experiencing clinically notable increases in pulse rates was highest in the iloperidone 8 mg b.i.d. (24%) and iloperidone 24 mg q.d. (23%), similar in the iloperidone 12 mg b.i.d. (11%) and quetiapine (14%) groups and lowest in the ziprasidone group (3%). The number of patients experiencing clinically notable increases in pulse rates during treatment period 2 decreased in all iloperidone treatment groups and continued to decrease in period 3. The number of clinically notable increases in pulse rates remained constant in treatment period 2 for both ziprasidone and quetiapine groups (Table 10-7).

The incidence of clinically notable decreases in systolic blood pressure was greatest in the iloperidone 8 mg b.i.d. in all three treatment periods (ILO 8 mg b.i.d.= 18%, 11%, and 8%, respectively; ILO 12 mg b.i.d. = 3%, 3%, and 3%, respectively; ILO 24 mg q.d. = 9% ,0%, and 3%, respectively; quetiapine = 6% and 3%, respectively; ziprasidone 0% and 0%). The incidence of clinically notable decreases in diastolic pulse was similar in all treatment groups.

Table 10-7 Number (%) of patients with clinically notable values for sitting 3-minute blood pressure and pulse rate by treatment period and by treatment (Safety population)

		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 (%)
Treatment Period 1		N=34	N=37	N=35	N=34	N=35
Pulse (BPM)	High	8 (24)	4 (11)	8 (23)	1 (3)	5 (14)
Systolic BP (mmHg)	High	0 (0)	0 (0)	0 (0)	1 (3)	1 (3)
	Low	6 (18)	1 (3)	3 (9)	0 (0)	2 (6)
Diastolic BP (mmHg)	High	1 (3)	0 (0)	1 (3)	1 (3)	4 (11)
	Low	1 (3)	1 (3)	1 (3)	0 (0)	0 (0)
Treatment Period 2		N=28	N=34	N=31	N=32	N=33
Pulse (BPM)	High	2 (7)	2 (6)	3 (10)	1 (3)	5 (15)
Systolic BP (mmHg)	High	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Low	3 (11)	1 (3)	0 (0)	0 (0)	1 (3)
Diastolic BP (mmHg)	High	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
	Low	2 (7)	2 (6)	1 (3)	1 (3)	0 (0)
Treatment Period 3		N=25	N=31	N=31	--	--
Pulse (BPM)	High	0 (0)	0 (0)	2 (6)	--	--
Systolic BP (mmHg)	High	0 (0)	0 (0)	0 (0)	--	--
	Low	2 (8)	1 (3)	1 (3)	--	--
Diastolic BP (mmHg)	High	0 (0)	0 (0)	0 (0)	--	--
	Low	1 (4)	0 (0)	0 (0)	--	--

N=number of patients with measures available for analysis; ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine; BPM=beats per minute; BP=blood pressure

Source: Post-text Table 10.4.1-3

Weight and body temperature

The incidence of clinically notable increases in weight was higher in the iloperidone 8 mg b.i.d. (13%) and iloperidone 24 mg q.d. (16%) groups than the iloperidone 12 mg b.i.d. (6%), ziprasidone 80 mg b.i.d. (6%), and quetiapine 375 mg b.i.d. groups (3%) (Table 10-8). The incidence of clinically notable increases in body temperature were similar across treatment groups.

Table 10-8 Number (%) of patients with clinically notable values for weight and body temperature, by treatment (Safety population)

		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 (%)
Weight (kg)		N=31	N= 34	N=32	N= 33	N=29
	High	4 (13)	2 (6)	5 (16)	2 (6)	1 (3)
	Low	5 (16)	4 (12)	3 (9)	5 (15)	2 (7)
Body temperature		N=34	N=37	N=35	N=34	N=34
(Degrees C)	High	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)

N=number of patients with measures available for analysis; ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine
Clinically notable weight=change from baseline of ≥7%; clinically notable temperature= ≥38.3 degrees C with change from baseline of ≥1.1 degrees C

Source: Post-text listing 10.4-2 Source: Post-text Table 10.4.2-2

10.5 Other safety evaluations

10.5.1 Summary of electrocardiogram (ECG) data

During Treatment Period 1, heart rate, obtained from ECG measurement, increases in all treatment groups. During Treatment Period 2, in all Iloperidone treatment groups heart rate returns to baseline (ILO 8 mg b.i.d.) or slightly below the baseline heart rate values (ILO 12 mg b.i.d. and 24 q.d.), and remains elevated in the ziprasidone and quetiapine treatment groups (Table 10-9).

In general, the mean changes from baseline in the RR interval corresponded to those observed for the heart rate change (Table 10-9).

Table 10-9 Summary of heart rate and RR interval data by treatment (Safety population)

ECG parameter (change from Baseline)	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.
Treatment Period 1 [b]	N=34	N=37	N=35	N=34	N=35
Heart rate (bpm)	7.6	7.7	5.3	4.7	10.9
RR interval (msec)	-77.9	-77.0	-52.4	-48.8	-110.8
Treatment Period 2 [b]	N=28	N=33	N=31	N=32	N=33
Heart rate (bpm)	-0.9	-3.9	-4.8	5.0	15.8
RR interval (msec)	9.2	42.9	65.9	-54.5	-153.5
Treatment Period 3 [b]	N=25	N=31	N=31	--	--
Heart rate (bpm)	-1.6	-4.7	-5.2	--	--
RR interval (msec)	15.9	47.9	68.2	--	--

N=number of patients with measures available for analysis; ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine
[a] Maximum positive (or least negative if no positive value for a given patient) minus baseline. Baseline value is obtained by averaging all values on Days –2, -1 and 0.
[b] Value at each treatment period is obtained by averaging all values within that treatment period.
Source: Post-text Table 10.5-1

Frequency of newly occurring or worsening ECG abnormalities (relative to baseline), based on eRT-specified criteria

ECG abnormalities which were newly occurring or worsened from baseline (baseline included all ECG recorded on Days –2, -1, and 0) were observed in 35%, 32%, and 46% of the iloperidone-treated patients in the 8 mg b.i.d., 12 mg b.i.d., and 24 mg q.d. groups, respectively and in 41% of ziprasidone and 40% of quetiapine-treated patients. No substantial differences were observed between treatment groups in individual newly occurring or worsening abnormalities (Table 10-10). None of these ECG findings were associated with cardiovascular AEs.

Further information concerning patients with newly occurring, or worsening from baseline, ECG abnormalities is presented in Post-text Filtered Listing 10.5-1.

Table 10-10 Number (%) of patients with newly occurring or worsening ECG abnormalities (relative to baseline) by treatment (Safety population)

ECG abnormality	ILO 8 mg b.i.d. N=34	ILO 12 mg b.i.d. N=37	ILO 24 mg q.d. N=35	ZIP 80 mg b.i.d. N=34	QUET 375 mg b.i.d. N=35
	n (%)	n (%)	n (%)	n (%)	N (%)
Total patients with any new or worsened ECG abnormality	12 (35)	12 (32)	16 (46)	14 (41)	14 (40)
T Waves: Flat	8 (24)	8 (22)	6 (17)	9 (26)	8 (23)
T Waves: Inverted	2 (6)	2 (5)	4 (11)	5 (15)	1 (3)
U Waves: Abnormal	2 (6)	2 (5)	3 (9)	0 (0)	1 (3)
First Degree Block	1 (3)	0 (0)	2 (6)	1 (3)	3 (9)
T Waves: Biphasic	1 (3)	0 (0)	3 (9)	1 (3)	1 (3)
ST Segment: Depressed	0 (0)	1 (3)	0 (0)	3 (9)	1 (3)
VPC	0 (0)	1 (3)	1 (3)	0 (0)	1 (3)
APC	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
Ectopic Atrial Rhythm	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
Left Anterior Hemiblock	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
WPW	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)

ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine; VPC=ventricular premature contractions; APC=atrial premature contractions; WPW=Wolff-Parkinson-White syndrome
Note: Baseline value is obtained by averaging over all measurements on days -2 , -1 and 0.
Source: Post-text Table 10.5-2

10.5.2 Clinical Global Impression of Severity of illness (CGI-S)

In this study, the Clinical Global Impression of Severity (CGI-S) scale was not used as an efficacy measure but rather to monitor the clinical status of patients for safety purposes. Results are summarized by treatment in Source: Post-text Table 10.5-3. At baseline the severity of illness was similar across treatment groups. Mean CGI-S scores did not change substantially from baseline to endpoint and were similar in all treatment groups.

Table 10-11 CGI-S: Mean (±SD) change from baseline score (Safety population)

	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=33	N=37	N=34	N=33	N=33
Baseline	3.5 ± 0.7	3.5 ± 0.7	3.4 ± 0.7	3.5 ± 0.8	3.5 ± 0.7
End point	3.2 ± 0.8	3.4 ± 0.8	3.3 ± 0.8	3.4 ± 0.9	3.3 ± 0.7
Change from baseline*	0.4 ± 0.7	0.1 ± 0.7	0.1 ± 0.6	0.1 ± 0.7	0.2 ± 0.6

N = number of patients with an evaluation post-baseline; ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine; CGI-S=Clinical Global Impression of Severity score
*Note: Change is calculated as endpoint minus baseline, so that a negative change indicates improvement.
Source: Post-text Table 10.5-3

10.6 Other evaluations: pharmacogenetic evaluations

The exploratory pharmacogenetic evaluations included in this trial were designed to investigate the association between genotypes and phenotypes. Neither genotypes nor phenotypes were pre-specified for this investigation. Hence, all statistical analyses performed were considered exploratory. The results from this exploratory analysis are reported separately.

11 Discussion and overall conclusions

11.1 Discussion

The effect of iloperidone on QTc has been evaluated in several Phase III trials. In the first two 6-week phase III trials that were conducted [ILP3000, ILP3004], doses of 2-8 mg b.i.d. were studied and mean changes in QTcF at endpoint were modest (≤5 msec) and similar to active comparators, risperidone (2.4 msec) and haloperidol (1.4 msec). Subsequently, doses of 6-8 mg b.i.d. and 10-12 mg b.i.d. of iloperidone were studied [Study ILP3005] and the mean changes in QTcF were higher in both iloperidone treatment arms than the active comparator, risperidone (ILO 6-8 mg b.i.d.=4.6 msec, ILO 10-12 mg b.i.d=8.5 msec, RIS=1.1 msec). In the current trial, which QTcF changes were measured at Tmax, iloperidone given as a b.i.d. regimen was associated with mean changes in QTcF that were similar to changes observed in patients treated with ziprasidone (~9 msec) and higher than mean changes observed in patients treated with quetiapine (~1 msec). When iloperidone was given as a once-daily dose regimen (24 mg q.d.), which is associated with higher peak plasma levels of iloperidone and P88, a greater mean change from baseline in QTcF was observed (15.4 +/- 11.7 msec). In comparison to the values that were obtained in a similar study (Study 054 conducted by Pfizer), the changes from baseline in QTcF for ziprasidone and quetiapine-treated patients were slightly higher in the current study. Nevertheless, the results of both studies consistently show ziprasidone to be associated with an increase from baseline in QTcF that was greater than quetiapine with the magnitude of the difference between the two compounds being similar.

The effect of metabolic inhibition on iloperidone and the active comparators was also assessed in this trial. Iloperidone is extensively metabolized through cytochrome P450 and

non-P450 mediated mechanisms. The primary active metabolite, P88, is reduced via alpha-reductase, which has no known metabolic inhibitors or inducers. The other major metabolite of iloperidone, P95, is formed via CYP2D6. A minor metabolite, P89, is form via metabolism through CYP3A4. During Treatment Period 2, the addition of paroxetine, a potent CYP2D6 inhibitor, to the regimen of iloperidone-treated patients was associated with a modest increase in peak plasma concentrations for iloperidone and P88. Correspondingly, a modest increase in QTcF values from Treatment Period 1 to Treatment Period 2 was observed for all iloperidone-treated patients. When ketoconazole was added to the treatment regimen of quetiapine-treated patients, a substantial increase (~300%) in plasma concentration of the parent drug was observed and was associated with only a modest increase in QTcF from Treatment Period 1 to Treatment Period 2. However, when ketoconazole was added to the regimen of ziprasidone-treated patients, a modest increase in plasma concentration was observed and was associated with a moderate increase in QTcF from Treatment Period 1 to Treatment Period 2 (9.9 to 15.9 msec).

In Period 3, when metabolism of a second P450 mediated pathway, CYP3A4, was inhibited via the addition of ketoconazole, a further substantial increase in peak plasma concentrations of iloperidone and P88 was observed. Coinciding with this increase in concentration of both parent and active metabolite, an increase in QTcF was observed for all iloperidone treatment groups. The largest increases in concentration of iloperidone and P88 were observed in the iloperidone 8 mg b.i.d. and iloperidone 12 mg b.i.d. groups, which were also associated with the largest increases in QTcF from Treatment Period 1 to Treatment Period 3. In the iloperidone 24 mg q.d. group, peak concentrations of iloperidone and P88 and change in QTcF from Treatment Period 1 to Treatment Period 3 increased but to a lesser extent.

In general, all doses of iloperidone and comparators treatment groups were well tolerated. Cardiovascular events were limited to cases of tachycardia most frequently in the Iloperidone 12 mg b.i.d. treatment group. The incidence of adverse events of tachycardia during Treatment Period 1 was higher in the iloperidone 12 mg b.i.d. group than the incidence reported for all other treatment groups. Increases in pulse rates are a well-characterized effect of antipsychotics with high affinity for the α_1 receptor, such as iloperidone. In this trial, two patients treated with iloperidone discontinued as a result of tachycardia. Both events occurred during titration (one of which was also reported as an SAE) and both patients recovered without sequela. This effect however was transient and does not appear to be concentration-related as no adverse events of tachycardia were observed in any iloperidone treatment group during Treatment Periods 2 or 3. Dizziness was reported during Treatment Period 1 at similar rate for iloperidone and quetiapine-treated patients and occurred very infrequently after period 1 (1 patient treated with ziprasidone during Treatment Period 2, 1 patient treated with iloperidone 12 mg b.i.d. treatment period 3). Hypotension was infrequently reported during the trial and no cases of syncope were reported. No adverse events related to prolongation of QTc interval were reported.

Data from all doses of iloperidone were combined to evaluate the pharmacokinetic/pharmacodynamic relationship between concentrations and QTcF values during each period. The slope of the concentration-effect relationship was substantially steeper for iloperidone and P88 in all periods in comparison to P95, which is consistent with preclinical data showing P95 to have very low affinity on the HERG channel (PK/PD Report

in Appendix 8.2.1, internal report for ChanTest Study 001016.OPW). Additionally, a statistical significant relationship between concentration and QTc effect was observed for iloperidone parent drug in Treatment Period 2 and for P88 in both Treatment Period 2 and 3. No statistically significant relationships between concentration and increases in QTc were observed for either ziprasidone or quetiapine. However both comparator treatment arms contained substantially fewer samples than the combined iloperidone data and thus a direct comparison across treatment arms for concentration-effect relationship is not possible.

In addition to analyzing mean changes in QTcF and PK/PD relationships to determine if iloperidone has an effect on QTc duration and thus cardiac repolarization, safety was assessed for individual patients utilizing outlier analysis. Although no specific clinical threshold exist at which torsades de pointes can be expected to occur, a relationship between increasing risk for torsades and changes in QTc values have been identified. Regulatory guidelines have suggested that values of greater than 500 msec and changes of greater than or equal to 60 msec are of clear clinical concern (CPMP guidelines). In this trial, no patients in any treatment arm experienced a QT or QTc (using any correction factor) value of greater than 500 msec. Seven patients in the iloperidone treatment arms experienced a change in QTc value of $\geq$ 60 msec at Tmax (10 patients overall in all secondary analyses). No patients in the quetiapine or ziprasidone treatment arms experienced changes of this magnitude. Therefore, although mean changes in QTc suggest iloperidone and ziprasidone have an effect on cardiac repolarization, the effect does not appear to cause a substantial number of patients to cross thresholds that are considered of clear clinical concern.

11.2 Conclusions

This study provides evidence that administration of iloperidone at doses of 16-24 mg/day is associated with a prolongation of the QT interval (8.5-15.5 msec). Mean change from baseline in QTcF at T_{max} was similar to ziprasidone 80 mg b.i.d. when iloperidone was administered at doses of 8-12 mg b.i.d. Administration of iloperidone 24 mg q.d. produced a greater effect on QTcF. Metabolic inhibition increased the effect of iloperidone on the QTcF duration especially when both the CYP3A4 and CYP2D6 pathways are inhibited. In the presence of both ketoconazole and paroxetine, the difference in mean change from baseline in QTcF at T_{max} between the twice daily and once daily regimens was minimal.

Administration of iloperidone 16-24 mg/day given as either a b.i.d. or q.d. regimen did not cause a substantial number of patients to experience QTc values or changes in QTc values that were of clear clinical concern.

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Novartis Pharmaceuticals Corporation
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Pharmacogenetics

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Pharmacogenetics study of CYP2D6 polymorphisms on Iloperidone concentration in study IL0522A2328

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List of abbreviations

Abbreviation	*Description*
A	Adenosine nucleotide
ANOVA	Analysis of Variance
AUC	Area under the Curve
C	Cytosine nucleotide
CYP2D6	Cytochrome P450 subfamillyIID, polypeptide 6
CYP3A4	Cytochrome P450 subfamillyIIIA, polypeptide 4
ECG	Electrocardiogram
G	Guanine nucleotide
HERG	Voltage Activated K^+ Channel (Human Eag related)
QT	The QT interval of the ECG waveform
QTc	Corrected QT value
QTcF	Fridericia correction of QT duration
T	Thymine nuclotide
TMax	Time at which maximum blood concentration is reached

1 Summary

The objective of the Pharmacogenetic analysis in study ILP2328 was to identify genetic polymorphisms that may be associated with risk for QT prolongation after treatment with Iloperidone.

This report presents association between genetic polymorphisms in the CYP2D6 locus and concentrations of Iloperidone and its metabolites in the course of the ILP2328 trial, a prospective, randomized, open label, 6 arm, parallel group study measuring the effect of iloperidone on QTc duration relative to baseline. The patients enrolled carried the diagnosis of either schizophrenia or schizoaffective disorder.

Blood samples for Pharmacogenetic analysis was collected at screening. Two polymorphisms previously associated with poor metabolizing status were genotyped in the CYP2D6 and 251 genotypes were collected. The individual genotypes were studied for detection of association between genotype class and concentrations of iloperidone and its metabolites P88 and P95. The functional effect of the polymorphisms was also evaluated by analyzing the effect of the addition of the CYP2D6 inhibitor paroxetine on the concentrations of the parent drug and its metabolites.

We have identified a significant association between CYP2D6 genotype and concentrations of P88 before the addition of inhibitors. In this report we discuss this finding and provide suggestions for interpreting these results in the context of QTc prolongation.

2 Introduction

Iloperidone is a benzisoxazole-piperidinyl derivative, currently in development for the treatment of schizophrenia. Data from placebo-controlled Phase III studies of iloperidone showed a QTcF increase of 0.1 to 8.5 msec at doses of 4-24 mg, when comparing a single ECG at baseline to a single ECG at endpoint. At lower doses of iloperidone (4 mg – 16 mg) QTc prolongation was minimal (0.1 – 5 msec). In the most recently completed iloperidone study, ILP3005, a greater prolongation was observed when higher doses of iloperidone (20-24 mg/day) were studied. The mean change in QTcF at doses 20-24 mg/day was 8.5 msec, and 4.6 msec in the 12-16 mg/day dose range in this study. These data suggest that treatment with iloperidone can be associated with prolongation of the QT interval similar to other drugs in this class, and that the effect may be dose sensitive in the clinical dose range.

ILP2328 was designed to examine the effect of different doses of iloperidone relative to the effect of ziprasidone and quetiapine on QTc duration under carefully controlled conditions. To further evaluate the possible relationship between exposure to iloperidone and the comparators to QTc duration, reassessment after pharmacological inhibition of the principle metabolic pathways for each drug, under steady-state conditions, was also planned.

Iloperidone is a substrate for two P450 enzymes; CYP2D6 and CYP3A4 and most metabolic clearance of iloperidone depends on these two enzymes. CYP2D6 catalyzes hydroxylation of the pendant acetyl group to form metabolite P94, which is converted to P95 after some additional reactions. Addition of the CYP2D6 inhibitor fluoxetine, along with iloperidone resulted in increases of the AUC for iloperidone and P88 of 131% and 119% respectively. Addition of the CYP3A4 inhibitor ketoconazole in interaction studies resulted in a 38-58% increase in the concentrations of iloperidone and its main metabolites P88 and P95. P88 has a pharmacological profile including affinity for the HERG channel similar to that of iloperidone. P95 is less lipophilic and is dissimilar in its binding profile compared to iloperidone, including having very low affinity for the HERG channel. For these reasons P95 is regarded as being pharmacologically inactive.

The addition of metabolic inhibitors in this study therefore allowed for an evaluation of the effect of increasing blood-concentration of iloperidone parent and/or its metabolites on QT duration.

For these reasons ILP2328 was designed to evaluate the effect of iloperidone on QTc before and after the addition of the CYP2D6 inhibitor paroxetine, as well as before and after the addition of the CYP3A4 inhibitor ketoconazole.

The CYP2D6 gene is highly polymorphic, with more than 70 allelic variants described so far (for more information see www.imm.ki.se/CYPalleles, DiAnne Bradford 2002). We have examined the two most common polymorphisms within the CYP2D6 gene in caucasian populations, CYP2D6G1846A and CYP2D6P34S. The CYP2D6G1846A represents a G to A transition at the junction between intron 3 and exon 4, shifting the splice junction by one base pair, resulting in frameshift and premature termination of the protein (Kagimoto 1990, Gough 1990, Hanioka 1990). The CYP2D6P34S is also known as CYP2D6C100T and represents a C to T change that results in the substitution of a Proline at position 34 by Serine (Yokota 1993, Johansson 1994). Both these polymorphisms have been associated with reduced enzymatic activity for different substrates (Johansson 1994, Dahl 1995, Jaanson 2002, see also review by Bertilsson 2002)

3 Methods

3.1 Samples

128 individuals from clinical trial ILP2328 consented to the pharmacogenetic study. Blood samples were collected according to the Pharmacogenetics protocol and after the consent of patients. The DNA was extracted from whole blood by Covance using the PUREGENE™ DNA isolation kit (D-50K).

The 128 individuals that participated were a good representation of the total sample of 165 individuals that participated in the trial. 22 of 29 total were from the Iloperidone 8 mg bid group, 30 of 34 were from the Iloperidone 12 mg bid group, 22 of 31 from the 24 mg qd

group, 3 of 5 of the Risperidone group, 28 of 33 of the Ziprazidone group and 23 of 33 of the Quetiapine group.

3.2 Genotyping

Genotypes for the CYP2D6G1846A polymorphisms were ascertained for 123 of the 128 consenting individuals, while genotypes for the CYP2D6C100T polymorphism were identified for all 128 participants. Genotyping was performed on amplified DNA fragments. The CYP2D6 genomic region was amplified using a triplex PCR strategy (Neville 2002). In brief, primers used were:

Exons 1 & 2	2D6L1F1:	CTGGGCTGGGAGCAGCCTC
	2D6L1R1:	CACTCGCTGGCCTGTTTCATGTC
Exons 3,4,5 &6	2D6L2F:	CTGGAATCCGGTGTCGAAGTGG
	2D6L2R2:	CTCGGCCCCTGCACTGTTTC
Exons 7,8 & 9	2D6L3F:	GAGGCAAGAAGGAGTGTCAGGG
	2D6L3R5B:	AGTCCTGTGGTGAGGTGACGAGG

Amplification was performed on 40-100ng of genomic DNA using a GC-rich PCR kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's recommendations. Thermocycling conditions were as follows: initial denaturation (3min 95°C), 10 cycles of 30s of denaturation (30s at 95°C), annealing (30s at 66°C), and extension, (60s at 72°C) followed by 22 cycles: 30s at 95°C, 30s at 66°C, 60s+5s/cycle at 72°C. A final extension followed (7min at 72°C).

Third Wave Technologies, Inc (Madison, WI) developed the probe sets for genotyping. Genotyping was performed on PCR products using the Invader® assay (Lyamichev 1999) (Third Wave Technologies, Inc) according to the manufacturer's recommendations.

The genotypes of individuals distributed among the three Iloperidone groups were not significantly different (Table 1A and1B).

Table 1-A: Genotype frequencies by Iloperidone dose class for CYP2D6P34S

Iloperidone dose group	Genotype			Total
	CC	CT	TT	
Ilo 8 mg bid	19[a]	2	1	**22**
Ilo 12 mg bid	23	6	1	**30**

Ilo 24 mg qd	15	6	1	**22**
Total	**57**	**14**	**3**	**74**

a: number of individuals

Table 1-B: Genotype frequencies by Iloperidone dose class for CYP2D6G1846A

Iloperidone dose group	Genotype			Total
	AA	**AG**	**GG**	
Ilo 8 mg bid	0	3	17	**20**
Ilo 12 mg bid	1	6	23	**30**
Ilo 24 mg qd	1	5	15	**21**
Total	**2**	**14**	**55**	**74**

3.3 Statistical Analysis

The genotype effect of the 2 CYP2D6 polymorphisms on period 1 concentrations was evaluated using the following ANOVA model. Concentrations of iloperidone, P88 and P95 at Period 1, without inhibitor, at the Tmax of the parent compound or metabolite were used as the dependent variable, the genotypes of each polymorphism as classes and the treatment as a covariate. In order to adjust for treatment effects after the single dose of Iloperidone, the 8 mg bid was coded as 8, the 12 mg bid as 12 and the 24 mg qd as 24.

The function of these polymorphisms on the degree of inhibition of the CYP2D6 enzyme was calculated from the ratio of concentrations of P88 and P95 in period 2, after the addition of the inhibitor of CYP2D6.

4 Results and Discussion

In order to understand the functional significance of the two CYP2D6 polymorphisms on the activity of the enzyme, we examined the association of the various genotypes with the relative concentrations of the metabolites P88 and P95. It is known that P88 is degraded by CYP2D6 and that CYP2D6 is involved in the synthesis of P95. The relative amounts of P88 and P95 would therefore be controlled by the activity of the CYP2D6 enzyme. We calculated the ratio of P88/P95 before inhibition in Period 1 and at the Tmax of the two metabolites, as well as the ratio of P88/P95 in Period 2 after the addition of the CYP2D6 inhibitor paroxetine. In

individuals with the wild type enzyme the concentration of P88 is expected to increase in Period 2, while in the same period the concentration of P95 is expected to decline.
For Period 1 the mean P88/P95 ratio among the 91 Iloperidone treated patients was equal to one with a wide range from 0.14 to 8.19. Among the same individuals for Period 2 the mean ratio was 2.4 with a range from 0.5 to 8.49. The mean ratio of the ratios Period 1/Period 2 was equal to 0.37 with a range from 0.11 to 2.75.
Among the genotyped individuals the values were similar with means of 1, 2.4 and 0.38 for Period 1, Period 2 and Period1/Period2 respectively, indicating no sample bias.
For polymorphism CYP2D6G1846A the means were significantly different between the three-genotype classes AA, AG and GG. For AA the respective values were 6, 3.4, and 1.8, for AG they were 2.4, 4.2, and 0.5 and for GG 0.57, 1.94 and 0.28 (Table 2).

Table 2: Ratios of P88, P95 concentrations according to genotype

Population	P88/P95 Period1		P88/P95 Period 2		P88/P95 (Period1/Period2)	
All	1.0	(0.14-8.19)	2.45	(0.50-8.49)	0.37	(0.11-2.75)
CYP2D6G1846A						
AA	6.1	(3.96-8.19)	3.41	(2.96-3.87)	1.89	(1.0-2.75)
AG	2.4	(0.44-7.0)	4.20	(2.2-7.57)	0.52	(0.14-1.28)
GG	0.57	(0.14-2.2)	1.94	(0.52-4.71)	0.28	(0.11-0.61)

The differences between genotype classes were significant at the $p<0.0001$ level in ANOVA test. These data suggest that the AA class represent a CYP2D6 poor metabolizer as indicated by the high ratio of P88/P95 in period 1 and the relatively small effect of the addition of the inhibitor in Period 2. The AG class seems to exhibit an intermediate phenotype between the poor metabolizer and the wild type with an approximately 2 fold reduction of the CYP2D6 activity after the addition of the inhibitor, as indicated by the ratio of the ratios (Table 2). This analysis provides a phenotypic characterization of the CYP2D6G1846A polymorphism as it relates to the metabolism of iloperidone.

Having established a functional role of this polymorphism we calculated the concentrations of P88 at Period 1 at the Tmax of P88 for each genotype class. P88 concentrations were significantly ($p<0.005$) higher for the AA and AG classes as compared to the GG class for each of the three Iloperidone dose groups (Table 3)

Table 3: P88 concentrations in Period 1 according to CYP2D6 genotype

Genotype	N obs	LSMeans	P value

AA	2	62.70	
AG	14	31.40	<0.0001
GG	55	21.03	
TRT dose			0.0015
CYP2D6G1846A *TRT dose			0.0058

Although number of individuals carrying the A allele is limited, the results obtained in the study consistently suggest that individuals of the AA and AG class are expected to experience higher concentrations of P88 at Tmax as compared with GG individuals.

Similar results were obtained with polymorphism CYP2D6P34S (Table 4 and 5).

Table 4: Ratios of P88, P95 concentrations according to genotype

Population	P88/P95 Period1		P88/P95 Period 2		P88/P95 (Period1/Period2)	
All	1.0	(0.14-8.19)	2.45	(0.50-8.49)	0.37	(0.11-2.75)
CYP2D6P34S						
CC	0.6	(0.14-2.28)	1.93	(0.52-4.71)	0.27	(0.11-0.61)
CT	2.2	(0.44-7.0)	4.14	(2.2-7.57)	0.49	(0.14-1.28)
TT	5.24	(3.56-8.19)	4.19	(2.96-5.74)	1.46	(0.62-2.75)

Table 5: P88 concentrations in Period 1 according to CYP2D6 genotype

Genotype	N obs	LSMeans	P value
CC	57	21.03	
CT	14	33.16	<0.0001
TT	3	51.00	
TRT dose			<0.0001
CYP2D6P34S *TRT dose			0.0015

This result is expected given the fact that this polymorphism is in almost complete linkage disequilibrium with the CYP2D6G1846A polymorphism.

In order to understand whether the difference in concentration of P88 at Period 1 Tmax was relevant to the increases in QTc after the addition of the inhibitors, we used the observed mean of P88 for the CYP2D6G1846A AG group to divide all individuals in 2 classes. The first includes individuals with P88 concentrations at Period 3, after the addition of both inhibitors, of equal to or less than 34 ng/ml and the second class includes individuals with

P88 concentration greater than 34 ng/ml. We then compared the two classes in regards to the QTc change from baseline at Period 3. Using an ANOVA statistic for the first class P88 > 34 (n = 55) the QTc mean change from baseline in Period 3 was 22.7 msec and that for P88 ≤ 34 (n = 12) the mean QTc for the same period was 7.7 msec. The QTc changes from baseline for Period 1 and Period 2 according to genotype and iloperidone dose are given in Table 6 and 7.

Table 6: QTc change at Period 1 according to CYP2D6 genotype and Iloperidone dose

	Iloperidone Dose		
Genotype	**8 mg bid**	**12 mg bid**	**24 mg qd**
CYP2D6G1846A			
AA		17.7 (1)[a]	38.4 (1)
AG	-0.8 (3)	5.8 (6)	19.0 (5)
GG	7.8 (17)	11.8 (23)	14.0 (14)
CYP2D6P34S			
TT	-8.4 (1)	17.7 (1)	38.4 (1)
CT	2.9 (2)	5.8 (6)	19.0 (5)
CC	7.8 (17)	11.8 (23)	9.5 (14)

a: number of individuals

Table 7: QTc change at Period 2 according to CYP2D6 genotype and Iloperidone dose

Genotype	Ilo 8 mg bid	Ilo 12 mg bid	Ilo 24 mg qd
CYP2D6G1846A			
AA		25.0 (1)	28.4 (1)
AG	8.1 (3)	8.7 (6)	20.6 (5)
GG	11.7(18)	14.5 (21)	16.4 (15)
CYP2D6P34S			
TT	-0.7 (1)	25.0 (1)	28.4 (1)
CT	12.5 (2)	8.7 (6)	20.6 (5)
CC	11.7(16)	14.5 (21)	16.4 (15)

These results however should be viewed with caution since the number of observations is small. If one was however to focus on the iloperidone 24 mg qd, there is a trend for higher QTc among AA, and AG individuals for CYP2D6G1846A as compared to GG. This difference disappear after the addition of the CYP2D6 inhibitor in Period 2.

These observations suggest that the differences in P88 concentrations during Period 1 between the different classes of genotypes may be relevant to QTc changes from baseline. Given the small number of observations and the unbalanced in regards to genotype design of the study, a confirmatory prospectively designed study may be required before any further interpretation of this data is warranted.

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ILOPERIDONE

IND No. 36, 827

CILO522A2328 PG Report: Single Nucleotide Polymorphisms in the *CYP2D6* Gene are Correlated with Iloperidone Drug Exposure Levels Impacting the Degree of QTc Prolongation Associated with Iloperidone Treatment

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CONFIDENTIAL

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List of Abbreviations

Abbreviation	Description
ANOVA	analysis of variance
b.i.d.	*bis in diem*/ twice-a-day
Cmax	maximum concentration
CYP	cytochrome P450
ECG	electrocardiogram
hERG	Human Ether-a-go-go related Gene
ILO	iloperidone
msec	millisecond
PG	pharmacogenetics
q.d.	*quaque die*/once-a-day
QT	the QT interval of the ECG waveform
QTc	corrected QT value
QTcF	Fridericia-corrected QT value
SNP	single nucleotide polymorphism
TdP	torsades de pointes
Tmax	time at which maximum blood concentration is reached

1 Summary

In an effort to identify genetic factors that may associate with treatment response to iloperidone, specifically QTc prolongation, we have examined polymorphisms in the *CYP2D6* gene from genetic samples taken from patients who participated in the CILO522A2328 clinical trial. We observed associations between the *CYP2D6*4* and *CYP2D6*10* polymorphisms and extent of iloperidone blood exposure levels and with QTc prolongation following iloperidone treatment. Individuals who are either nonGG for *CYP2D6*4* or nonCC for *CYP2D6*10* are more likely to experience longer prolongations of the QTc interval following iloperidone treatment versus individuals with the other corresponding genotypes. To better understand exposure to total active compound, we correlated the ratio of the combined concentrations of iloperidone and P88 to P95 (i.e. active vs. inactive drug) with the extent of QTc prolongation observed after iloperidone treatment. Importantly, we have identified a significant association between the (iloperidone+P88)/P95 ratio and QTc prolongation ($p=0.046$). These results indicate that patients who have an (iloperidone+P88)/P95 ratio <4 experience less prolongation of the QTc interval versus patients who have a ratio ≥ 4. These results offer a potential risk management strategy and prospective testing tools for physicians when treating patients with iloperidone if the potential for QTc prolongation is considered to be a risk to the patient's safety.

2 Introduction

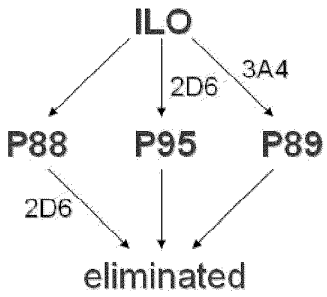
An area of focus in the evaluation of drug safety is the effect on non-cardiac medications on the QT interval of the electrocardiogram (ECG). It is thought that the primary mechanism of action by which non-cardiac medications prolong the duration of the QTc interval is through inhibition of the Human Ether-a-go-go related Gene (hERG) channel, a potassium channel directly involved in ventricular repolarization. The clinical significance of the magnitude of effect on QTc (corrected QT) duration observed with these compounds continues to be debated. According to preliminary research, treating physicians are not concerned about the QTc prolongation potential of antipsychotic medications. However, QTc prolongation and its relationship to torsades de pointes arrhythmia[1] has received increased attention from regulatory authorities, resulting in warnings on the label.

Antipsychotics, both typical and atypical, have been associated with an increase in the duration of the QTc interval[2]. A study comparing the effect of several antipsychotics on the QTc duration showed thioridazine to be associated with the highest degree of QTc prolongation, followed by ziprasidone[3]. Quetiapine, risperidone, olanzapine, and haloperidol were also associated with a prolongation of the QTc interval[3]. In this study, a minimum increase in QTc was observed when metabolic inhibitors of the CYP450 isoenzyme responsible for the metabolism of each respective drug. An exception was observed with haloperidol, which resulted in a doubling of QTc with metabolic inhibition.

As has been seen with other antipsychotics, iloperidone has been observed to have some effects on QTc duration[4]. Mean change from baseline in QTcF at T_{max} was similar to ziprasidone 80 mg b.i.d., the recommended starting dose for ziprasidone according the package insert, when

iloperidone was administered at doses of 8-12 mg b.i.d. [4]. Metabolic inhibition by adding an inhibitor of CYP2D6 increased the effect of iloperidone on the QTcF duration[4]. As a potential risk-minimization strategy, and to help physicians manage iloperidone's potential for prolonging the QTc interval, Vanda is committed to identifying inherited genetic factors that may predispose patients to be more susceptible to experience QTc prolongation which may be deemed clinically significant by the treating physician. By providing physicians tools to help identify patients prospectively before the first dose of iloperidone, the physician will be able to make a more educated decision on 1) whether to prescribe iloperidone for this patient, 2) the dose for this patient to minimize the potential of a QTc prolongation, and 3) how often to schedule ECGs to monitor for potential QTc prolongation.

Figure 1: Metabolism of iloperidone



	Inhibition of:		
	2D6	3A4	2D6+3A4
ILO	↑	↑	↑↑
P88	↑	↑	↑↑
P95	↓	↑	↓

As stated previously, iloperidone is metabolized by CYP2D6, as well as CYP3A4 to produce to two main metabolites, P88 and P95, and one metabolite (P89) that is quickly eliminated (Figure 1). When CYP2D6 is inhibited, levels of iloperidone and P88 increase and P95 decrease. Because iloperidone was shown to prolong the QTc interval in the clinical, functional binding studies were performed to determine the affinity of iloperidone and its two main metabolites to the hERG channel. The results shown in Table 1[5] demonstrate a strong affinity for iloperidone and P88 towards the hERG channel, and weak affinity for P95. Therefore, iloperidone and P88 are considered to be potential active moieties and P95 to be inactive with respect to iloperidone's propensity to prolong the QTc interval.

Table 1:hERG channel affinities of iloperidone, P88 and P95

Test Article	hERG IC50 (nM) @ 22 °C	hERG IC50 (nM) @ 34-35 °C
Iloperidone	29	37
P88	4,319	12,789
P95	56	100

Results from pharmacokinetic/pharmacodynamic modeling results from the thorough QTc study (CILO522A2328) have suggested that iloperidone's QTc prolongation may be correlated with Cmax levels of iloperidone[4]. The *CYP2D6* gene is highly polymorphic, with more than 70 allelic variants described thus far (see http://www.cypalleles.ki.se/). Vanda has examined the two most common polymorphisms within the *CYP2D6* gene in Caucasian populations, *CYP2D6G1846A* and *CYP2D6C100T*, which results in a "poor metabolizer" phenotype and thus higher circulating drug levels in the blood. The *CYP2D6G1846A* polymorphism represents a G to A transition at the junction between intron 3 and exon 4, shifting the splice junction by one base pair, resulting in frameshift and premature termination of the protein[6-8]. The *CYP2D6C100T* polymorphism, also known as CYP2D6P34S, represents a C to T change that results in the substitution of a proline at position 34 by serine[9;10]. Both these polymorphisms have been associated with reduced enzymatic activity for different substrates[9;11;12]. Therefore, we examined these polymorphisms for correlation with iloperidone exposure and iloperidone-induced QT prolongation. The following report summarizes the findings.

3 Methods

128 individuals from clinical trial CILO522A2328 consented to the pharmacogenetic study. Blood samples were collected according to the Pharmacogenetics protocol and after the consent of patients. The 128 individuals that participated were a good representation of the total sample of 165 individuals that participated in the trial. 22 of 29 total were from the iloperidone 8 mg b.i.d. group, 30 of 34 were from the Iloperidone 12 mg bid group, 22 of 31 from the 24 mg q.d. group[13]. Genotyping was performed on PCR products using the Invader® assay[14] (Third Wave Technologies, Inc) according to the manufacturer's recommendations.

All analyses were performed using SAS Enterprise Guide version 4.0 (Cary, North Carolina). To aid in power, all iloperidone treatments and certain genotype classes were pooled together. The genotype effect of potential polymorphisms was analyzed using data from period 1 of the trial, where no metabolic inhibitors were present, using the following ANOVA model. QTcF changes from baseline at the Tmax of iloperidone were used as the dependent variable, sex, age, race, and an adjusted baseline value were used as quantitative (covariate) variables, and the genotypes of each polymorphism, or the (iloperidone+P88)/P95 ratio classification as classes. LSMeans results are reported using the Bonferroni correction method for all pairwise tests.

4 Results and Conclusions

Pharmacokinetic/pharmacodynamic modeling results from CILO522A2328 suggest that iloperidone's QTc prolongation may be correlated with Cmax levels of iloperidone[4]. To determine if polymorphisms in the *CYP2D6* gene are correlated with QTc prolongation, we first investigated possible associations with the *CYP2D6*4(G1846A)* polymorphism. As shown in Table 2, patients who had two copies of the wild-type allele (G) had the least amount of QTc

prolongation compared to patients who had either one or two copies of the polymorphic allele (A), the allele which results in coding for a truncated, inactive CYP2D6 protein. Comparison of patients with two copies of the wild-type allele (GG) to those who did not (nonGG), showed a trend towards significance, indicating a possible interaction between *CYP2D6*4(G1846A)* and QTc prolongation following iloperidone treatment. Similar trends were observed when the analysis was broken down by treatment, but small sample sizes did not allow for enough power to detect statistically significant differences.

Table 2: *CYP2D6*4 (G1846A)* polymorphism is association with QTcF change from baseline following iloperidone treatment

Genotype	Number of Patients	LSMeans QTcF Change from Baseline (msec)
GG	52	11.1
GA	14	15.9
AA	2	41.6

Genotype	Number of Patients	LSMeans QTcF Change from Baseline (msec)	P Value
GG	52	11.1	0.0594
nonGG	16	18.5	

We next investigated possible associations with the *CYP2D6*10(C100T)* polymorphism. As shown in Table 3, patients who had two copies of the wild-type allele (C) had the least amount of QTc prolongation compared to patients who had either one or two copies of the polymorphic allele (T), the allele which results in coding for a truncated, inactive CYP2D6 protein. Comparison of patients with two copies of the wild-type allele (CC) to those who did not (nonCC), showed a significant difference in the amount of QTc prolongation experienced following iloperidone treatment. Similar trends were observed when the analysis was broken down by treatment (8 mg b.i.d., 12 mg b.i.d., 24 mg q.d.), but small sample sizes did not allow for enough power to detect statistically significant differences.

Table 3: *CYP2D6*10 (C100T)* polymorphism is association with QTcF change from baseline following iloperidone treatment

Genotype	Number of Patients	LSMeans QTcF Change from Baseline (msec)
CC	54	10.8
CT	14	16.9
TT	3	31.3

Genotype	Number of Patients	LSMeans QTcF Change from Baseline (msec)	P Value
nonCC	54	10.8	0.0281
CC	17	19.2	

Study CILO522A2328 demonstrated that C_{max} levels of iloperidone correlated with increases in QTc. Thus, minimizing C_{max} levels of iloperidone may minimize the QTc prolongation potential of iloperidone. Because iloperidone exposure levels are regulated by CYP2D6, this suggests that CYP2D6 intermediate (corresponding to the *CYP2D6*4 GA* and *CYP2D6*10 CT* genotypes) and poor metabolizers (corresponding to the *CYP2D6*4 AA* and *CYP2D6*10 TT* genotypes) should have their iloperidone doses reduced to minimize high C_{max} levels.

To better understand exposure to total active compound, we correlated the ratio of the combined concentrations of iloperidone and P88 to P95 (i.e. active vs. inactive drug/metabolite) with the extent of QTc prolongation observed after iloperidone administration. As shown in Table 4, the (iloperidone+P88)/P95 ratio was 1.0 in CYP2D6 extensive metabolizers (corresponding to the *CYP2D6*4 GG* and *CYP2D6*10 CC* genotypes), 3.9-4.1 in CYP2D6 intermediate metabolizers (corresponding to the *CYP2D6*4 GA* and *CYP2D6*10 CT* genotypes), and 9.8-12.0 in CYP2D6 poor metabolizers (corresponding to the *CYP2D6*4 AA* and *CYP2D6*10 TT* genotypes). Table 4 also demonstrates a proportional relationship between the (iloperidone+P88)/P95 ratio QTc prolongation. Because CYP2D6 intermediate and poor metabolizers would experience higher plasma levels of iloperidone, we investigated if there was a correlation between the extent QTc change and an (iloperidone+P88)/P95 ratio. Patients with a ratio <4, had a least squares mean change of 10.7 msec, while patients with a ratio ≥ 4, had a mean change of 20.2 (p=0.046). These results suggests that monitoring a patient's (iloperidone=P88)/P95 ratio, and adjusting their dose to obtain a ratio <4, may be a possible risk-management strategy for iloperidone.

Table 4: Correlation of CYP2D6 genotype on the (iloperidone+P88)/P95 ratio and least squares mean QTcF change from baseline

CYP2D6 Genotype	(Iloperidone+P88)/P95 Ratio	Least Squares Mean QTcF Change From Baseline (msec)
CYP2D6*4 GG (N=52)	1.0	11.7
CYP2D6*4 GA (N=14)	3.9	14.1
CYP2D6*4 AA (N=3)	12.0	32.9
CYP2D6*10 CC (N=54)	1.0	11.5
CYP2D6*10 CT (N=14)	4.1	15.7
CYP2D6*10 TT (N=3)	9.8	23.7

Table 5 Least squares mean QTcF change from baseline correlates with (iloperidone+P88)/P95 ratio

(iloperidone+P88)/P95 Ratio	Least Squares Mean QTcF Change From Baseline (msec)	P Value
Ratio < 4 (N=81)	10.75	0.0468
Ratio ≥ 4 (N=10)	20.23	

These results indicate that patients who carry the wild-type alleles for either *CYP2D6*4* or *CYP2D6*10* experience less prolongation of the QTc interval following iloperidone treatment compared to patients that carry the polymorphic alleles for either *CYP2D6*4* or *CYP2D6*10*. In addition, a statistically significant association exists between iloperidone, P88 and P95 blood levels and QTc prolongation. These results offer a potential risk management strategies and prospective testing tools for physicians when treating patients with iloperidone, by either testing a patient's genotype for *CYP2D6* or monitoring iloperidone exposure levels, if the potential for QTc prolongation is considered to be a risk to the patient's safety.

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