ERRATA

DATE: 24 MAY 2007

From: NAMITA GANDHI, CLINICAL RESEARCH SCIENTIST, VANDA PHARMACEUTICALS INC, 9605 MEDICAL CENTER DRIVE SUITE, 300 ROCKVILLE, MD 20850

RE: CORRECTION TO CLINICAL STUDY REPORT ILO522 0104

The following error(s) exist in Report ILO5220104:

- Page 34, Table 7.4-4 for PK parameter $t_{1/2}$ (hr) % difference was incorrectly reported in this table. The correct value should be 86.4 (instead of 88.3). In addition, the value for Ae (% of dose) should be 55.6 instead of 35.7.

- Page 43, Table 7.4-10 for the PK parameter $AUC_{0-\infty}$ (ng*hr/ml) % difference was incorrectly reported in this table. The correct value should be 9.6 (instead of -9.6) based on the formula calculation presented in the footnote of this table.

- Page 72, Section 1.3.3 refers to Appendix 11. This appendix is not contained in this document.

In addition, the following documents were not provided by the originator for this study report:

- Page 2, signatures for the clinical study report
- Appendix 2: Laboratory quality assurance (QA) procedures

- Page 5, Appendix 5a, signatures for DMPK R98-1825

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Clinical Pharmacology

ILO522

Study No. CILO522 0104

An open-label study to characterize the pharmacokinetics of iloperidone in poor and extensive 2D6 metabolizers and to evaluate the interaction of iloperidone with a cytochrome P450 2D6 prototype substrate (dextromethorphan) in healthy subjects

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1.1 Signatures

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Approved:

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1.8 List of abbreviations

AE	adverse event
AHA	American Heart Association
ALT	alanine aminotransferase
ART	adverse reaction terminology (dictionary)
AST	aspartate aminotransferase
AUC	area under the concentration time curve
AV	atrioventricular
b.i.d.	bis in diem / twice a day
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
C_{max}	maximum plasma concentration
CL_T/F	apparent clearance (corrected for absolute bioavailability)
CPK	creatine phosphokinase
CRF	case report / record form
CRO	Contract Research Organization
CS&E	Clinical Safety and Epidemiology
CYP2D6	cytochrome P450 2D6
CYP3A4	cytochrome P450 3A4
DEX	dextromethorphan
ECG	electrocardiogram
ED_{50}	effective dose (the dose at which 50% of the maximum effect is reached)
EM	extensive cytochrome P450 2D6 metabolizer
FDA	Food and Drug Administration
GCP	good clinical practice
γ-GT	gamma-glutamyl-transpeptidase
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
IEC	Independent Ethics Committee
ILO	iloperidone
IND	Investigational New Drug application

IRB	Institutional Review Board
ITD	International Therapy Dictionary
i.v.	intravenous(ly)
LDH	lactate dehydrogenase
mm Hg	millimeters of mercury
NCS	not clinically significant
NOAEL	no-observable adverse effect level
NTEL	no-toxic-effect level
q.d.	once a day
pH	negative log hydrogen ion concentration
PD	pharmacodynamics
PK	pharmacokinetics
PM	poor cytochrome P450 2D6 metabolizers
PR	pulse rate
p.o.	per os / by mouth / orally
RBC	red blood cells (erythrocytes)
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase (same as AST)
SGPT	serum glutamic pyruvic transaminase (same as ALT)
SOP	Standard Operating Procedures
t_{max}	time to reach C_{max}
$t_{½}$	elimination half-life
TBD	to be determined
V_z/F	volume of distribution (corrected for absolute bioavailability)
WBC	white blood cells (leukocytes)
WHO	World Health Organization

1.9 Study personnel

1.9.1.1 Key Novartis personnel

Clinical Pharmacology Study Leader	Marilyn White, MPH
Clinical Pharmacology Physician	Greg Sędek, MD
Clinical Pharmacokineticist	Somesh Choudhury, PhD
Study Biostatistician	Peiming Ma, PhD
Bioanalyst	Michael Hayes, PhD
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1.9.1.2 External personnel

Principal Investigator	Thomas Hunt, MD PPD Pharmaco, Inc. 706 Ben White Blvd. Austin, Texas 78704
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2 Study synopsis

Title of study: An open-label study to characterize the pharmacokinetics of iloperidone in poor and extensive 2D6 metabolizers and to evaluate the interaction of iloperidone with a cytochrome P450 2D6-prototype substrate (dextromethorphan) in healthy subjects

Investigator(s): Thomas Hunt, MD, PPD Pharmaco, Inc.

706A Ben White Blvd. Austin, Texas 78704

Publication(s): None

Study period: first subject dosed 03-Oct-98 last subject completed 13-Apr-99

Objectives:

To compare the elimination patterns of iloperidone and its metabolites in subjects genotyped as poor vs. extensive CYP2D6 metabolizers

To assess the pharmacokinetic interactions of iloperidone and dextromethorphan in subjects genotyped as extensive CYP2D6 metabolizers

Design:

This was a two-cohort, randomized, open-label, three-period crossover study. Healthy subjects identified by genotyping as extensive CYP2D6 metabolizers were enrolled in Cohort 1 and healthy subjects identified by genotyping as poor CYP2D6 metabolizers were enrolled in Cohort 2.

Subjects in Cohort 1 participated in a screening period, a baseline period (repeated prior to each treatment period), three treatment periods, and a study completion evaluation. In Period 1, all subjects received a single dose of 3 mg iloperidone. In Periods 2 and 3 subjects received 80 mg dextromethorphan and 3 mg iloperidone + 80 mg dextromethorphan in a sequence determined by a randomization scheme. Iloperidone plasma samples were collected for 72 hours after administration of iloperidone and iloperidone + dextromethorphan. Dextromethorphan serum samples were collected for 24 hours after administration of dextromethorphan alone and 72 hours after administration of iloperidone + dextromethorphan. Subjects were discharged from the unit after the last PK sample was drawn in each period. All subjects in Cohort 1 had a 7 day washout between treatments.

Subjects in Cohort 2 participated in a screening period, a baseline period, one treatment period, and a study completion evaluation. Subjects received a single 3 mg dose of iloperidone. Plasma samples were collected for 72 hours after dosing. Subjects were discharged from the study after the last PK sample was drawn.

Number of subjects: Nineteen (19) subjects were identified by genotyping as extensive CYP2D6 metabolizers (EM). Eight (8) subjects were identified by genotyping as poor CYP2D6 metabolizers (PM). Twenty seven subjects were entered (19 EM and 8 PM). Twenty six subjects completed (18 EM and 8 PM). One (1) subject dropped out due to an adverse event.

Criteria for inclusion: Healthy male and female subjects genotyped as extensive or poor metabolizers between the ages of 18 and 45

Investigational drug:

Iloperidone: 1 mg capsules, Batch # F0170498

Benylin® Adult Formula (*Dextromethorphan)*: 15mg/5ml, Lot # 24558L, Manufacturer: Parke-Davis

Duration of treatment: Cohort 1: 3 periods with 2 single doses of 3 mg iloperidone and 2 single doses of 80mg dextromethorphan given

Cohort 2: one period with a single 3 mg iloperidone dose given

Criteria for evaluation:

Safety and tolerability: Medical history, physical examination, vital signs, ECG, laboratory evaluations (biochemistry, hematology, urinalysis), and adverse event monitoring.

Pharmacokinetics: Plasma and urine concentrations of Iloperidone and its metabolites P88-8991 and P95-12113. Serum concentrations of dextromethorphan and its metabolite dextrorphan.

Statistical methods: An analysis of variance (ANOVA) model based on a parallel group design was used to compare iloperidone, P88-8991, and P95-12113 PK profiles between Cohort 2 and Cohort 1 (first period). The model was fitted to the log-transformed PK parameters.

An ANOVA model based on a 2×2 crossover design was used to compare dextromethorphan and dextrorphan PK profiles from Periods 2 and 3. The model was fitted to the log-transformed PK parameters. An ANOVA model based on a randomized block design was used to compare iloperidone, P88-8991, and P95-12113 PK profiles from all three periods.

Results:

Safety and tolerability:

Adverse events (AEs) were reported by 20 of 27 subjects. The most common adverse events suspected to be related to the study medications were dizziness, rhinitis, tachycardia, headache, nausea, and vomiting. The frequency of AEs in the Cohort 2 (PM) was not significantly different than the frequency in Cohort 1 (EM). However, the number of AEs per subject was higher in Cohort 1 (EM) than in Cohort 2 (PM). There were less AEs reported when iloperidone and dextromethorphan were given in combination (n=14) versus iloperidone given alone (n=39) in Cohort 1. One subject (03) withdrew after the first dose due to a primary adverse event of anxiety.

Pharmacokinetics:

Extensive vs. Poor CYP2D6 Metabolizers

Though the mean C_{max} of iloperidone in extensive metabolizers (2.79 ng/mL) was only slightly higher than in poor metabolizers (2.26 ng/mL), the exposure to iloperidone as measured by $AUC_{0-\infty}$ was 57% more in poor metabolizers (46.3 ng*hr/mL) than in extensive metabolizers (29.4 ng*hr/mL). The elimination half-life in poor metabolizers was prolonged by 88%. Since the apparent volume of distribution of iloperidone was similar in both populations, this prolongation of the half-life of iloperidone in poor metabolizers was due to a 43% decrease in the apparent clearance of iloperidone. The amount of unchanged iloperidone excreted in urine was negligible (0.45% and 0.70% of the administered dose in extensive and poor metabolizers, respectively).

The mean C_{max} of P88-8991, one of the metabolites which is formed via reduction of iloperidone, was increased by 44% from 2.32 ng/mL in extensive metabolizers to 3.33 ng/mL in poor metabolizers. The $AUC_{0-\infty}$ of P88-8991 also increased by 95% in poor metabolizers (mean of 96.4 vs. 49.4 ng*hr/mL). The terminal elimination half-life was prolonged to 37.5 hr in poor metabolizers in comparison to 25.5 hr in extensive metabolizers. Although the amount of drug excreted in urine as metabolite P88-8991 was increased from 4.2% of administered dose in extensive metabolizers to 8.0% in poor metabolizers, the renal clearance remained similar between extensive (46.5 mL/min) and poor (51.3 mL/min) metabolizers.

The maximum concentration of P95-12113, another metabolite formed via CYP2D6 isozyme metabolism, was decreased significantly (by 87%) in poor metabolizer (4.5 vs 0.67 ng/mL). This decrease in C_{max} was also reflected in $AUC_{0-\infty}$, which was decreased by 80%. The elimination half-life was prolonged from 23 hr in extensive metabolizers to 30.6 hr in poor metabolizers. The amount of drug excreted in urine as

metabolite P95-12113 was also significantly less (76%) in poor metabolizers. In spite of smaller amount of metabolite being excreted in urine, the renal clearance of P95-12113 remained similar in both population (66.4 mL/min in extensive metabolizers vs 75.0 mL/min in poor metabolizers).

Effect of Dextromethorphan on Iloperidone pharmacokinetics

The mean plasma concentration vs. time profiles for iloperidone, following administration of iloperidone alone and in combination with dextromethorphan, were superimposable. The mean maximum concentration of iloperidone following administration of iloperidone alone (2.79 ng/mL) and in combination with dextromethorphan (2.75 ng/mL) appeared at the same median time of 2.5 hr. The pharmacokinetic parameters of iloperidone were similar between both treatments. The differences in C_{max}, $AUC_{0-\infty}$, $t_{½}$, CL_T/F, and V_z/F between the two treatments were less than 4.0%.

The mean plasma concentration vs. time profiles of P88-8991 following administration of iloperidone alone and in combination with dextromethorphan were essentially identical. The maximum concentration of the metabolite appeared in the plasma at the same time. The differences in C_{max}, $AUC_{0-\infty}$, and $t_{½}$ between the two treatments were less than 7.0%.

The mean plasma concentration vs. time profiles of P95-12113 following administration of iloperidone alone and in combination with dextromethorphan were also indistinguishable. The formation and clearance of the metabolite were similar between treatments. The differences in C_{max}, $AUC_{0-\infty}$, Ae, and CL_R between the two treatments were less than 6%, and the difference in $t_{½}$ was about 13.0%.

Effect of Iloperidone on Dextromethorphan's pharmacokinetics

Dextromethorphan was absorbed quickly with a similar median t_{max} of 2 hrs following both treatments of dextromethorphan alone and in combination with iloperidone. There was a 24% increase in the mean C_{max} value of dextromethorphan (7.0 vs. 8.68 ng/mL), however there was only a 9.6% increase in $AUC_{0-\infty}$ following combination treatment. The differences in $t_{½}$, CL_T/F, and V_z/F were less than 10%.

The metabolite dextrorphan, formed via CYP2D6 metabolism of dextromethorphan, was formed quickly and at the same rate with a median t_{max} of 2 hrs following both treatments, dextromethorphan alone and in combination with iloperidone. The differences in C_{max} (1049 vs. 996 ng/mL) and $AUC_{0-\infty}$ (5776 vs. 5833 ng*hr/mL) between the treatments were less than 5%. However, concomitant administration of iloperidone increased the elimination half-life of dextrorphan by 58% (4.55 vs. 7.17 hr).

Conclusions:

Exposure to iloperidone and P88-8991 was significantly increased ($AUC_{0-\infty}$ by 57% and 95%, respectively), while exposure to P95-12113 was significantly decreased ($AUC_{0-\infty}$ by 80%) in poor CYP2D6 metabolizers compared to extensive CYP2D6 metabolizers.

Poor and extensive CYP2D6 metabolizers tolerated the drug similarly and there were no safety concerns in either population.

In extensive metabolizers, dextromethorphan did not alter the pharmacokinetics of iloperidone; changes in dextromethorphan pharmacokinetics when a 3 mg dose of iloperidone was coadministered appeared to be too small to be of clinical relevance. Thus, an interaction between iloperidone and other CYP2D6 substrates is unlikely.

Iloperidone and dextromethorphan were tolerated when given together or alone, with no clinically significant findings in the safety assessments.

Date of the report:

3 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 subjects, 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.

4 1. Introduction

Schizophrenia is a severe mental illness that affects an estimated 1% of the world's population. Patients suffer from productive symptoms (e.g., hallucinations and delusions) and deficit symptoms (e.g., blunted affect and social withdrawal), as well as impairment of cognitive functions. The pharmacological antagonism of central dopamine D_2 receptors by classical antipsychotics (e.g., chlorpromazine, haloperidol) has been demonstrated to be effective in treating productive symptoms, although this antagonism is also associated with extrapyramidal side effects, tardive dyskinesia, and elevations in prolactin levels.

With the advent of clozapine, there has been a shift from the concept of pure dopamine D_2 blockade, to one of a combined antagonism of serotonin $5HT_2$ and dopamine D2 receptors. The discovery of new pharmacological agents, which exhibit a more balanced, mixed $D_2/5HT_2$ antagonism, has resulted in a new generation of improved therapeutic agents (e.g., risperidone) that are effective not only against productive symptoms but also deficit and cognitive symptoms of schizophrenia. These antipsychotics demonstrate enhanced tolerability with respect to extrapyramidal symptoms and diminished propensity for elevations in prolactin levels.

Iloperidone is a mixed $D_2/5HT_2$ antagonist with preferential affinity for $5HT_{2A}$ receptors in humans classifying it as a novel antipsychotic. Iloperidone shares some pharmacologic characteristics with clozapine, risperidone, olanzapine, and ziprasidone. Iloperidone also exhibits an affinity for human dopamine D_3 receptors and for rat serotonin $5HT_6$ receptors, properties that may confer some additional therapeutic advantages in the treatment of schizophrenia. Clozapine has been demonstrated to bind with high affinity to sites that closely resemble $5HT_6$ serotonin receptors. The dopamine D_3 receptor is primarily present in the nucleus accumbens with very low levels in the caudate and putamen. Taken together, these binding characteristics indicate that iloperidone may result in enhanced control of psychotic symptoms with relatively little additional liability for inducing extrapyramidal symptoms.

Iloperidone is extensively metabolized in the liver and is primarily eliminated via renal excretion. *In vitro* human liver microsome studies and *in vivo* human ADME data indicate that iloperidone undergoes metabolism via at least three metabolic pathways: reduction, hydroxylation (mediated by

CYP2D6), and *O*-demethylation (mediated by CYP3A4). In previous studies in humans, the main component in plasma was the reduced metabolite, P88-8991, which has an AUC 70-90% greater than that of the parent compound. The P89-9124 metabolite, resulting from *O*-demethylation via CYP3A4, was only a minor component in plasma. Data from the human ADME study indicate that the CYP2D6 pathway may play a more important role than originally thought. In this study the major urinary components were P88-8991 and P95-12113, a metabolite formed along the CYP2D6 pathway. Since CYP2D6 is known to be polymorphic, with approximately 7-10% of the Caucasian population categorized as poor metabolizers of this isozyme, this study was conducted to evaluate whether or not there are differences in the elimination of iloperidone in subjects genotyped as extensive or poor metabolizers of CYP2D6. However, since iloperidone undergoes metabolism via at least three metabolic pathways and the combination of P88-8991 and P95-12113 in urine still only accounted for approximately 7-12% of the administered dose, differences arising due to CYP2D6 polymorphism were not expected to have a significant affect on total clearance of iloperidone.

In addition, the potential for drug-drug interactions will be explored in this study by using dextromethorphan hydrobromide as a CYP2D6 prototype substrate. The metabolism of dextromethorphan is very rapid and extensive, and primarily via the CYP2D6 pathway. A single oral dose of 80 mg of dextromethorphan HBr allowed assessment of a potential drug interaction in the CYP2D6 pathway.

A 3 mg dose was chosen for two reasons. Earlier studies indicated that this is the maximum single oral dose that could be tolerated by normal healthy volunteers and also this is the minimum single dose for which a pharmacokinetic profile can be elucidated (due to assay limitations at that time).

5 2. Study objectives

- To compare the elimination patterns of iloperidone and its metabolites in subjects genotyped as poor vs. extensive CYP2D6 metabolizers
- To assess the pharmacokinetic interaction of iloperidone and dextromethorphan in subjects genotyped as extensive metabolizers

6 3. Investigational plan

6.1 3.1. Study design

This was a two-cohort, randomized, open-label, three-period crossover study. Healthy subjects identified by genotyping as extensive CYP2D6 metabolizers were enrolled in Cohort 1 and healthy subjects identified by genotyping as poor CYP2D6 metabolizers were enrolled in Cohort 2.

All subjects underwent a screening period. Subjects in Cohort 1 participated in a baseline period (repeated prior to each treatment period), three treatment periods, and a study completion

evaluation. In each period, a standardized breakfast was served 50 minutes prior to dosing and was completed 30 minutes prior to dosing. Subjects received a single dose of 3 mg iloperidone in Period 1; in Period 2 and 3 subjects received 80 mg dextromethorphan and 3 mg iloperidone + 80 mg dextromethorphan in random order. Iloperidone plasma samples were collected for 72 hours after administering iloperidone and loperidone + dextromethorphan. Dextromethorphan serum samples were collected for 24 hours after administering dextromethorphan alone and for 72 hours after administration of iloperidone + dextromethorphan. Subject activity was restricted for the first 10 hours after dosing to minimize adverse events that were expected due to iloperidone's alpha blocking effects. Subjects were discharged from the unit after the last PK sample was drawn in each period. All subjects in Cohort 1 had a 7 day washout between treatments.

Subjects in Cohort 2 participated in a baseline period, a treatment period, and a study completion evaluation. Subjects received a light breakfast 50 minutes prior to dosing and were to be completed 30 minutes prior to dosing. Subjects received a single 3 mg dose of iloperidone. Plasma samples were collected for 72 hours after dosing.

The treatment design consisted of a two sequence design for Cohort 1 and a one sequence design for Cohort 2.

Table 3.1-1. Treatment Design

	Period 1	Period 2	Period 3
Cohort 1/Sequence 1	iloperidone	dextromethorphan + iloperidone	dextromethorphan
Cohort 1/Sequence 2	iloperidone	dextromethorphan	dextromethorphan + iloperidone
Cohort 2/Sequence 1	iloperidone		

The potential for drug-drug interactions was explored in this study by using dextromethorphan hydrobromide as a CYP2D6 prototype substrate. The metabolism of dextromethorphan is very rapid and extensive, and primarily via the CYP2D6 pathway.

6.2 3.2. Study population

Nineteen subjects were genotyped as extensive CYP2D6 metabolizers and eight subjects were genotyped as poor CYP2D6 metabolizers. All subjects were between the ages of 18 and 45 years. Female subjects were either postmenopausal or surgically sterilized at least 6 months prior to screening. Subjects were in good health as determined by past medical history, physical examination, electrocardiogram, laboratory tests, pregnancy test (female subjects), and urinalysis. All subjects were non-smokers.

6.3 3.3. Treatments

6.3.1 3.3.1. Investigational drug

Novartis provided the investigator with iloperidone 1-mg capsules. Sufficient quantities of investigational drug were administered: two 3-mg doses (3 x 1-mg capsules) to 18 subjects in Cohort 1 and one 3-mg dose (3 x 1-mg capsules) to 8 subjects in Cohort 2 and one subject in Cohort 1.

The investigator purchased Benylin® (dextromethorphan HBr) Adult Formula, by Parke-Davis; 15 mg/5mL. All ten bottles of the dextromethorphan had identical lot numbers and expiration dates.

Drug name	Identifier	Form	Unit Dose	Quantity
Iloperidone	Batch # F0170498 KN# 3753381	Capsules	1 mg	264 capsules
Benylin® Adult Formula (dextromethorphan HBr)	Lot # 24558L	Elixir	15mg/5ml	10 bottles x 120 ml/btl (1200ml total)

Details regarding the labeling of study medication and storage requirements can be found in the Study Protocol (Appendix 1).

Study center personnel administered study medication with 200 mL of water. Subjects were instructed not to chew the medication, but to swallow it whole. The investigator checked each subject's mouth to ensure the medication was swallowed.

All subjects were dosed in sequential order by subject number. Drug administration in individual subjects was to occur at approximately the same time in all treatments. Unless performing a study assessment, subjects were to rest quietly in a semi-recumbent position for 4 hours after dosing.

6.3.2 3.3.2. Blinding

This was an open-labeled study.

6.3.3 3.3.3. Treatment assignment

Subjects who met all study criteria during baseline evaluations were sequentially assigned a subject number within their cohort. For Cohort 1 (extensive metabolizers), subjects were numbered from 01 to 18. The replacement for Subject 03 was assigned number 103.Treatment sequences for each subject number were outlined in the randomization schedule (Appendix 1). For Cohort 2 (poor metabolizers), subjects were numbered from 19 to 26.

6.3.4 3.3.4. Concomitant therapy

Except for medication required to treat adverse events, no medication other than study drug was allowed from the initial day of screening until all of the final study evaluations had been completed. Administration of acetaminophen was acceptable but had to be documented in the CRFs. Decisions

regarding replacements of subjects requiring concomitant medication had to be discussed with the sponsor on a case by case basis. The administration of any such medication (including over-the-counter medications and vitamins) was to be clearly documented in the CRF.

6.3.5 3.3.5. Treatment compliance

Compliance was assured by administration of the study drugs under the supervision of the investigator or his/her deputy, and was verified by determinations of iloperidone and its metabolites, P88-8991 and P95-12113, in plasma and urine. Dextromethorphan compliance was verified by determinations of dextromethorphan and its metabolite, dextrorphan, in serum.

6.4 3.4. Study schedule and assessments

To determine eligibility to participate in the study, each subject was to undergo a screening evaluation within -2 to -21 days prior to dosing in Period 1. Screening evaluations included a past medical history, physical exam, ECG, vital signs, body temperature and weight, laboratory safety evaluations (hematology, biochemistry, urinalysis), pregnancy test (female subjects), urine drug and cotinine screens, hepatitis B, C and HIV serologies, and genotyping of CYP2D6 metabolism.

Baseline was defined as the period of a subject's continuous presence at the study facility to 30 minutes prior to administration of the study drug, before each of the three treatment periods. Baseline assessments included a review of the inclusion/exclusion criteria and past medical history, in order to verify the subject still met entry criteria. An assessment of current medical conditions, a physical examination, laboratory safety tests, vital signs, urine cotinine, pregnancy, and a drug screen were performed and reviewed for study inclusion/exclusion criteria prior to dosing. Safety evaluations were also used to determine any clinically significant changes after dosing.

Each treatment period started 30 minutes prior to dosing and consisted of a 72-hour on-site observation period for iloperidone PK blood sampling and a 24-hour on-site observation period for dextromethorphan PK blood sampling. During the treatment periods, subjects fasted the night prior to dosing and remained fasting until dosing. The appropriate treatment was administered according to the randomization schedule (iloperidone alone, iloperidone + dextromethorphan, or dextromethorphan alone). Treatment periods were separated by a washout interval of 7 days.

The study completion evaluation was performed after the last PK sample in Period 3 in Cohort 1 and Period 1 in Cohort 2. This evaluation included a physical exam, ECG, vital signs, pregnancy test (female subjects), and safety labs.

The study schedule and the assessments required during the study were delineated in Post-text Table 11.1-1. All assessment procedures are described in detail in the Study Protocol contained in Appendix 1.

6.4.1 3.4.1. Study conditions and restrictions

Subjects were confined to the study center for at least 12 hours before administration of study drug until 72 hours postdose in the iloperidone and iloperidone + dextromethorphan periods, and for 24 hours postdose in the dextromethorphan alone period.

During recruitment, informed consent review, and baseline period, the subjects had to observe with the following restrictions:

- No strenuous physical exercise (e.g., weight training, aerobics, football) for 7 days before dosing until after the study completion evaluation.
- No alcohol for 72 hours before dosing until after the study completion evaluation.

All subjects had to fast for at least 10 hours prior to the dose of study medication and continue to fast for at least 4 hours thereafter. Lunch and dinner were served at ~1300 and 1730, respectively, and a large snack was served at 2100 while domiciled.

During waking hours, subjects were required to have a fluid intake of at least 200 mL every 4 hours in addition to fluid taken with the medication.

Intake of xanthine (e.g., caffeine) containing food or beverages had to be discontinued 48 hours before dosing. Consumption of these foods and beverages (i.e., coffee, tea, soda, chocolate) was not permitted at any time while the subjects were domiciled.

6.4.2 3.4.2. Background and demographic assessments

The assessment of background, administrative and demographic data included a check of the inclusion/exclusion criteria, a medical history, recording of current medical conditions, date of birth, sex, race, height, elbow breadth and frame size. The laboratory screens required for entering the study consisted of a routine clinical chemistry and hematology screen, urinalysis, screens for drugs of abuse (e.g., alcohol, benzodiazepines, amphetamines, cannabinoids, cocaine, and opiates), hepatitis B and C, HIV, cotinine, genotyping of CYP2D6 metabolism, and pregnancy tests in female subjects. Drug administration records, meal records, the study completion information, records of repeat and additional evaluations and any comments were documented throughout the study as required by the Study Protocol. Details can be found in the Study Protocol and the sample Case Report Forms provided in Appendix 1.

6.4.3 3.4.3. Safety assessments

Safety assessments included the monitoring and recording of all adverse events and serious adverse events, regular checks of routine blood chemistry, hematology and urine values, ECG recordings, measurements of vital signs, and physical examinations. Details on these assessments can be found in the Study Protocol and the sample Case Report Forms provided in Appendix 1.

6.4.4 3.4.4. Pharmacokinetic assessments

Seven (7) milliliters (mL) of venous blood were drawn from the subject's forearm vein to determine iloperidone plasma concentrations at the following times: predose, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours post iloperidone dose(s).

Thirty (30) mL aliquots of urine were obtained for analysis during the following intervals: 0-8, 8-16, 16-24, 24-48, and 48-72 hours post iloperidone dose(s).

Five (5) mL of venous blood were drawn from the subject's forearm vein (into red topped tubes without a serum separator) to determine dextromethorphan serum concentrations at the following times: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hrs post dextromethorphan administered alone and predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours post dextromethorphan and iloperidone administered in combination.

All samples were processed as described in the Study Protocol (Appendix 1) and kept frozen at $\leq$ -70°C pending analysis.

7 4. Deviations from investigational plan

7.1 4.1. Protocol amendments

Amendment 1: 16-Oct-98

The protocol was amended to expand the study population eligibility and increase recruitment of both extensive and poor CYP2D6 metabolizing healthy subjects. The exclusion criteria were relaxed to include subjects who donated or lost 400 mL or more of blood between 1 to 3 months prior to dosing. Only those who donated or lost 400 mL or more of blood within 1 month prior to dosing were excluded.

7.2 4.2. Other deviations from protocol

7.2.1.1 Selection of subjects

Subjects were enrolled in the study with values for orthostatic changes outside the allowable limits without investigator or sponsor review. The investigational center's internal SOP's for subject enrollment required investigator's review and discretion on a case-by-case basis only if the vital signs of both supine and standing were out of range. The protocol's inclusion criteria requested reviewing subjects at investigator discretion if there was a >20 mm Hg decrease of systolic pressure, >10 mm Hg drop in diastolic blood pressure, or >20 bpm increase in pulse rate.

7.2.1.2 Adherence to evaluation schedule

Vital signs were repeated if out of range at standing only instead of both supine and standing.

7.2.1.3 Adherence to treatment regimen

Subject 25 on day –26 and Subject 26 on day –11 were administered dextromethorphan by the study center at screening due to a testing error.

8 5. Data management and quality control

8.1 5.1. Clinical data collection, database management and quality control

Investigators entered the information required by the protocol onto the Novartis Case Report Forms (CRFs) that were printed on 3-part, no carbon required (NCR) paper. Novartis monitors reviewed the CRFs for completeness and accuracy, and instructed site personnel to make any required corrections or additions. The CRFs were forwarded to the Medical Documents Reception Center of Novartis by Novartis monitors or by the investigational site, one copy was retained at the investigational site. The CRFs were received by Novartis and their receipt was to be recorded, the original copy was to be placed in Central Files and the NCR copy was forwarded to the responsible medical data management staff for processing. If CRFs were sent directly to Novartis by investigational sites, they were reviewed prior to data entry.

Data items from the CRFs were entered into the study database using double data entry with verification upon second entry. Text items (e.g. comments) were entered once and checked manually against the CRFs.

Subsequently, the information entered into the database was to be systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors were corrected by Novartis personnel. Other errors or omissions were entered on Data Query Forms, which were returned to the investigational site for resolution. A copy of the signed Data Query Form was kept with the CRFs, and once the original was received at Novartis, the resolutions were entered into the database. Quality control audits of all key safety and efficacy data in the database were made after entering data from each visit.

Concomitant medications were entered into the database and were coded using a WHO Anatomical Therapeutic Chemical dictionary. Coexistent diseases and adverse events were coded using a modified version of the WHO Adverse Reaction Terminology (ART) dictionary. All medications were classified and a code assigned by site of action, and therapeutic and chemical characteristics, using the WHO Anatomical Therapeutic Chemical (ATC) dictionary.

Laboratory samples were processed through a central laboratory, PPD Pharmaco and the results were sent electronically to Novartis.

When the database was declared 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.

8.2 5.2. Bioanalytical data management and quality control

Samples and Sample Log Forms were shipped by the investigator to the Bioanalytics and Pharmacokinetics (BAPK) Section of Novartis. Analysis was performed by means of LCMS. Details on the analytical methodology, the method validation and the analytical within-study quality control procedures and data are provided in the Bioanalytical Data Report (Appendix 5).

The final bioanalytical raw data (concentration and actual sampling time data) were transferred by BAPK to the Clinical Pharmacokineticist in the format of a password-protected Excel file. These data are the basis for all pharmacokinetic results in this report.

9 6. Data evaluation and statistical methods

All data was analyzed by Novartis Pharmaceuticals personnel. Detailed information on safety evaluations and statistical methods are located in Appendices 3 and 6, respectively.

9.1 6.1. General statistical considerations

9.1.1.1 Sample size determination

Sample size was determined by practical considerations.

9.1.1.2 Changes in the planned analyses

Descriptive statistics were only provided for demographic data, not for vital signs or ECGs.

9.2 6.2. Analysis of background and demographic data

Demographic variables such as age, weight, height, gender, and race by cohort and treatment are provided for all subjects who received at least one treatment.

9.3 6.3. Safety and tolerability evaluations

All subjects who received at least one treatment were included in the safety and tolerability evaluation.

9.3.1 6.3.1. Adverse events

All information obtained on adverse events is displayed by subject and by treatment in Appendix 3.

9.3.2 6.3.2. Clinical laboratory variables

All abnormalities are listed by subject and by treatment in Appendix 3. Out of range serum chemistry, hematology and urinalysis values were evaluated for clinical significance.

9.3.3 6.3.3. Vital signs

Vital signs were examined for abnormal values (and relevant orthostatic changes) for each subject and such occurrences identified by subject and treatment.

9.3.4 6.3.4. Electrocardiographic evaluation

ECG abnormalities are listed by subject and treatment in Appendix 3, Table 6-1.

9.3.5 6.3.5. Statistical methods

Descriptive summary statistics are provided for the demographic data. There was no inferential statistical analysis performed for the data.

9.4 6.4. Pharmacokinetic evaluations

All completed subjects were included in the pharmacokinetic data analysis.

Plasma and urine concentrations for iloperidone, its metabolites, P88-8991 and P95-12113, plus serum concentrations for dextromethorphan and its metabolite, dextrorphan, are expressed in mass per volume units. All concentrations below the limit of quantitation or missing data are labeled as such in the concentration data listings (see Appendix 5). Concentrations below the limit of quantitation were treated as zero in summary statistics and for the calculation of pharmacokinetic parameters. Descriptive statistics of pharmacokinetic parameters include mean, SD, and CV. Since the t_{max} parameter is generally evaluated by a nonparametric method, median values and ranges are given for this parameter.

Pharmacokinetic parameters were determined using non-compartmental method using WinNonlin Pro (Version 2.1).

9.4.1 6.4.1. Pharmacokinetic variables

All subjects who have completed PK profiles for iloperidone were included in the pharmacokinetic data analysis. Plasma and urine concentrations of iloperidone, P88-8991, P95-12113, plus serum concentrations for dextromethorphan and dextrorphan were used to determine the following pharmacokinetic parameters using non-compartmental methods.

AUC_{0-t}: Area under the concentration-time curve (AUC) from time zero to the last measurable sampling time point, calculated by linear trapezoidal method.

$AUC_{0-\infty}$: AUC from time zero to time infinity. This is calculated as $AUC_{0-t} + C_t/\lambda_z$ where C_t is the concentration at time t, and λ_z is the terminal elimination rate constant.

λ_z: Terminal elimination rate constant. The value of λ_z is determined from the slope of the regression line of lnC vs time with the following constraints: (i) there should be at least three consecutive measurable concentrations, (ii) all concentrations should be declining with time and (iii) the correlation coefficient (r) of regression should be ≥ 0.90.

C_{max}: Maximum concentration observed postdose.

t_{max}: Time at which the C_{max} occurs.

$t_{½}$: Elimination half-life, determined as $0.693/\lambda_z$.

CL_T/F: Apparent clearance of parent drug: $Dose/AUC_{0-\infty}$, where F is the bioavailability.

CL_T/f_m * F:	Apparent clearance of metabolite: Dose/$AUC_{0-\infty}$, where F is the bioavailability of the drug and f_m is the fraction of metabolite formed.
V_z/F :	Apparent volume of distribution of parent drug: Dose/(AUC* λ_z), where F is the bioavailability. (this term is also known as V_{area}).
V_z/f_m * F :	Apparent volume of distribution of metabolite: Dose/(AUC* λ_z), where F is the bioavailability and f_m is the fraction of metabolite formed. (this term is also known as V_{area}).
Ae	Total amount excreted in urine.
CL_R	Renal clearance: $Ae/AUC_{0-\infty}$

9.4.2 6.4.2. Statistical methods

Both plasma and urine data were used to derive PK parameters by the noncompartmental method. An analysis of variance (ANOVA) model was used to study the derived PK parameters after logarithmic transformation.

Let y be a log-transformed PK parameter of interest. The scheme of the ANOVA model here assumes that y follows the statistical relationship

$$y = \mu + \text{fixed/random effects} + \text{error},$$

where

- μ is the overall average of y.
- 'fixed/random effects' is a sum of fixed and/or random effects, depending on the objective being addressed. The random effects are normally distributed with mean 0.
- 'error' is a random variable, normally distributed with mean 0.

For the validity of the ANOVA, standard model-checking procedures were carried out to ensure no violation of assumptions.

9.4.2.1 Comparing the pharmacokinetics of iloperidone between poor and extensive CYP2D6 metabolizers

An ANOVA model based on a parallel group design was used to compare the PK profiles of iloperidone, P88-8991, and P95-12113 between Cohort 2 and the first period of Cohort 1. The model was fitted to the log-transformed PK parameters AUC_{0-8}, AUC_{0-t}, C_{max}, CL_R, CL_T/F, and Ae_{0-t}, when available.

In the ANOVA relationship described above, the fixed/random effect becomes 'genotype': poor (Cohort 2) vs. extensive (Cohort 1) metabolizers.

Cohort 2 was compared to Cohort 1 using the ESTIMATE statement in the SAS MIXED procedure. The 90% confidence intervals for the differences in the least-square means between Cohort 2 and Cohort 1 were calculated first. Taking antilogarithms, the confidence limits of ratio on the original scale were obtained.

Wilcoxon's rank sum test was used to compare t_{max} between the two cohorts.

9.4.2.2 Effect of dextromethorphan on the pharmacokinetics of iloperidone

An ANOVA model based on a randomized block design was used to compare the PK profiles of iloperidone, P88-8991, and P95-12113 from all three periods in Cohort 1. The log-transformed PK parameters AUC_{0-8}, AUC_{0-t}, C_{max}, CL_R, CL_T/F, and Ae_{0-t} were analyzed.

In the ANOVA relationship described above,

fixed/random effect = subj + trt

where 'subj' is a random subject effect and 'trt' is a fixed treatment effect: iloperidone and dextromethorphan vs. iloperidone alone.

To compare the test (iloperidone and dextromethorphan) and the reference (iloperidone alone) treatments, the 90% confidence intervals for the ratio of the least square means of the two treatments were constructed using the same method described in Section 6.4.2.1.

The non-parametric Wilcoxon's signed rank test for paired differences of t_{max} between the two treatments (iloperidone in combination with dextromethorphan vs. iloperidone alone) was performed.

9.4.2.3 Effect of iloperidone on the pharmacokinetics of dextromethorphan

An ANOVA model based on a 2-by-2 crossover design was used to compare the PK profiles of dextromethorphan and dextrorphan from Periods 2 and 3 in Cohort 1. The model was fitted to the log-transformed PK parameters AUC_{0-8}, AUC_{0-t}, C_{max}, and CL_T/F.

In the ANOVA relationship described above,

fixed/random effect = seq + subj(seq) + trt + per

where 'seq' is a fixed sequence effect, 'subj(seq)' is a random subject-within-sequence effect, 'trt' is a fixed treatment effect (iloperidone and dextromethorphan vs. dextromethorphan alone), and 'per' is a fixed period effect (Period 2 vs. 3).

The test treatment (iloperidone and dextromethorphan) and the reference treatment (dextromethorphan alone) were compared using the ESTIMATE statement in the SAS MIXED procedure. Similar to the method in Section 6.4.2.1, the 90% confidence intervals for the ratios of the least square means between the test and reference treatments were calculated.

In addition, the non-parametric Wilcoxon's signed rank test was performed for paired differences of t_{max} between the two treatments (iloperidone in combination with dextromethorphan vs. dextromethorphan alone).

10 7. Results

10.1 7.1. Subject disposition

A total of 27 subjects (19 in Cohort 1, 8 in Cohort 2) underwent baseline and at least one dosing period; 26 subjects (18 in Cohort 1, 8 in Cohort 2) completed the study. Subject 03 in Cohort 1 did not participate in Period 2 due to adverse events in Period 1.

10.2 7.2. Background and demographic results

10.2.1 7.2.1. Relevant medical history and current medical conditions

None of the subjects' medical histories were directly relevant to the outcome of the study nor to the interpretation of the results. A detailed listing of all subjects' medical histories and concomitant diseases at screening are listed in Appendix 3, Table 2-1.

10.2.2 7.2.2. Medications at screening and baseline

Subjects were requested not to take prescription drugs for at least one month prior to the first dosing or over the counter medications for at least 14 days. Subject 11 took Advil on Day -7 for a headache and Subject 13 took ibuprofen on Day -13 for a headache. Novartis and the investigator approved both.

Subject 25 on Day -26 and Subject 26 on Day -11 were administered dextromethorphan by the study center due to a testing error. This was discussed with Novartis and the investigator, and it was decided that the two subjects could be entered into the study at a later date.

A detailed list of prior and concomitant medications is provided in Appendix 3, Table 2-2.

10.2.3 7.2.3. Demographic data

The subject population consisted of 25 males (17 in Cohort 1, 8 in Cohort 2) and 2 females (Cohort 1) with a mean (±SD) age of 29.84 (± 6.09) years. Caucasians comprised 66.6% (n=18) of the total population (52.6%, n=10, Cohort 1/100%, n=8, Cohort 2), blacks comprised 3.7% (n=1) of the total population (5.3%, n=1, Cohort 1), Asians comprise 3.7% (n=1)of the total population (5.3%, n=1, Cohort 1) and other racial origins comprised 25.9% (n=7)(36.8% (n=7) Cohort 1). The mean (±SD) height and weight were 178.73 (±7.19) cm and 75.49 (±8.64) kg, respectively (Appendix 3, Table 2-4).

10.2.4 7.2.4. Genotyping

Subjects were genotyped and divided into cohorts accordingly. Nineteen subjects were enrolled in Cohort 1 and eight subjects were enrolled in Cohort 2. Subject 02 was genotyped as an extensive metabolizer, however the phenotype displayed in this study was like a poor metabolizer. The subject was re-genotyped with a more sensitive assay, which also indicated the subject to be an extensive metabolizer. Please see the pharmacokinetic section (Section 7.4.2) for detailed information on the analysis of PK data from this subject.

10.3 7.3. Safety and tolerability results

10.3.1 7.3.1. Serious adverse events

No serious adverse events or deaths were reported during the trial.

10.3.2 7.3.2. Adverse events

Adverse events were reported by 20 of 27 subjects (Appendix 3, Table 3-1). The most common adverse events suspected to be related to study medication were dizziness (16 episodes in 12 subjects), rhinitis (10 episodes in 8 subjects), tachycardia (5 episodes in 4 subjects), headache (5 episodes in 5 subjects), nausea (4 episodes in 3 subjects) and vomiting (2 episodes in 2 subjects).

Table 7.3-1. Adverse Events

Adverse Events	Number of episodes/subjects			
	Iloperidone alone		Dextromethorphan	Iloperidone + dextromethorphan
	Cohort 2 (n=8)	Cohort 1 (n=19)	Cohort 1 (n=19)	Cohort 1 (n=19)
dizziness	2/2	9/8	-	5/5
rhinitis	2/2	5/5	-	3/3
tachycardia	1/1	4*/3	-	-
headache	-	2/2	1/1	2*/2
nausea	-	3/3	-	1/1
vomiting	-	2/2	-	-
*one event not suspected to be related to study drug				

One subject (03) withdrew after the first dose due to a primary adverse event of anxiety. The subject had numerous adverse events coinciding with the anxiety. The other AEs included dizziness, dry mouth, rigors, fatigue which were suspected to be related to the study drug and tachycardia and dyspnea which were not suspected to be related to the study drug. Subject 03 was treated for anxiety and followed 83 days post-study. His anxiety was not suspected to be related to the study drug.

The frequency of adverse events reported by poor CYP2D6 metabolizers (5 in 8 PMs) was not significantly different than those reported by extensive CYP2D6 metabolizers (15 in 19 EM) when iloperidone was given alone (determined using a hypothesis test for proportions [Z-test], $p>0.2$). However, the number of AEs per extensive metabolizer was double that of the poor metabolizers. Within Cohort 1 (EM), the number of AEs reported after taking iloperidone with dextromethorphan (14 AEs in 8 subjects) was less than after taking iloperidone alone (39 AEs in 11 subjects). Only one adverse event was reported after taking dextromethorphan alone.

10.3.3 7.3.3. Concomitant medications due to adverse events

There were no concomitant medications taken while subjects were in the study.

10.3.4 7.3.4. Clinical laboratory findings

Laboratory evaluations were conducted at all baseline visits, prior to each treatment period and at study completion. The frequency of laboratory abnormalities in the poor CYP2D6 metabolizers was not significantly different than those in the extensive CYP2D6 metabolizers. The number of laboratory abnormalities (outside the expanded normal ranges) between the treatments in Cohort 1 was virtually the same (4 after iloperidone alone, 5 after dextromethorphan alone, and 6 after iloperidone plus dextromethorphan). This is not taking into consideration that some subjects had lab abnormalities outside the normal ranges before being dosed with any medication. No clinically significant abnormalities were reported; no subject was excluded from continued participation in the study due to a laboratory abnormality. Individual data are listed in Appendix 3. Abnormal values were flagged and are listed by subject and visit and by laboratory test in Appendix 3, Tables 4-2A, B, and C.

10.3.5 7.3.5. Vital signs

Blood pressure and pulse were measured at all baseline visits, all treatment periods and at study completion. Assessments were taken either after 3 minutes in a supine position or at both 3 minutes in a supine and standing position to assess orthostatic changes. (See Post text table 11.1-1 for the evaluation schedule).

Values outside the normal range for systolic and diastolic blood pressures and radial pulse were observed in both the supine and standing position during the course of the study (Appendix 3, Table 5-2). Values ranged from 76 to 140 mmHg for systolic blood pressure (normal range: 90-140 mmHg) and from 48 to 96 mmHg for diastolic blood pressure (normal range: 50-90 mmHg).

Elevated pulse rate measurements were more common, readings ranged from 48 to 118 bpm (normal range: 45-90 bpm).

Many of the subjects (both EM and PM) had increased pulse rates after standing post iloperidone doses (both alone and in combination). This is expected with standing and more so when given with iloperidone, which has alpha-receptor blocking effects.

Subject 03 had an increased pulse rate of 48 bpm between Baseline 1, and 4 hours post dose (58 to 106 bpm, repeat 116 bpm). The subject's pulse remained increased at 12 hours post dose (97 bpm) and remained above their baseline value (58 bpm) at study completion (72 bpm). There were no other symptoms of orthostatic hypotension. The subject withdrew from the study due to anxiety.

10.3.6 7.3.6. Electrocardiographic findings

ECG evaluations were conducted at screening, all baseline visits, and study completion. Subjects 13 and 14 were enrolled in the study with ECG abnormalities. Sponsor and investigator approval was given. Subject 13 had mild nonspecific T wave changes at screening and throughout the study. Subject 14 had mild right axis deviations at screening, Baseline 1, 2, and 3. Subject 103 had a normal ECG during the study and sinus bradycardia at study completion.

10.4 7.4. Pharmacokinetic results

10.4.1 7.4.1. Assay performance

10.4.1.1 Iloperidone, P88-8991, and P95-12113 assay performance in plasma

The calibration curves were linear ($y = a + b*x$) with a coefficient of correlation higher than 0.991 for all three analytes. The calibration curve model used was weighted linear regression with a weighting factor of $1/x^2$ for iloperidone and P88-8991 and $1/y^2$ for P95-12113.

Within-study assay validation was performed by analysis of QC samples together with the study samples. The range of quality control samples and their corresponding accuracy and precision were 0.104-104.0 ng/mL, 97-107% and 4.6-13.8% for iloperidone, 0.198-198.0 ng/mL, 99-101% and 3.9-10.2% for P88-8991 and 0.4-400 ng/mL, 97-101%, and 7-11% for P95-12113, respectively. The results are presented in Table 7.4-1.

Table 7.4-1. Summary of within-study assay validation in plasma

10.4.1.2 Iloperidone in plasma

Nominal conc. in QC Sample [ng/mL]	Number of Determinations	Mean Recovery [% of nominal conc.]	Precision* [%]
0.104	9	102.0	13.8
0.207	7	97.3	8.53
51.8	9	107.0	5.24
104	9	104.0	4.61

10.4.1.3 P88-8991 in plasma

Nominal conc. in QC Sample [ng/mL]	Number of Determinations	Mean Recovery [% of nominal conc.]	Precision* [%]
0.198	9	99.0	10.2
0.396	7	99.1	8.21
99.0	9	101.0	5.74
198.0	9	100.0	3.98

10.4.1.4 P95-12113 in plasma

Nominal conc. in QC Sample [ng/mL]	Number of determinations	Mean Recovery [% of nominal conc.]	Precision* [%]
0.400	9	98.8	9.35
0.800	8	101.0	11.1
200.0	8	98.0	9.12
400	8	97.5	6.65

* coefficient of variation: (100 • standard deviation/mean)

The limit of quantitation for plasma analysis was 0.05 ng/mL for iloperidone, 0.1 ng/mL for P88-8991 and 0.2 ng/mL for P95-12113. For details on assay performance see Appendix 5.

10.4.1.5 Iloperidone, P88-8991, and P95-12113 assay performance in urine

The calibration curves were linear ($y = a + b*x$) with a coefficient of correlation higher than 0.992 for all three analytes. The calibration curve model used was weighted linear regression with a weighting factor of $1/x^2$.

Within-study assay validation was performed by analysis of QC samples together with the study samples. The range of quality control samples and their corresponding accuracy and precision were 0.207-104.0 ng/mL, 102-118% and 4.2-13.0% for iloperidone, 0.396-198.0 ng/mL, 100-108% and 3.5-7.7% for P88-8991 and 0.8-400 ng/mL, 102-107% and 3.5-9.8% for P95-12113, respectively. The results are presented in Table 7.4-2.

Table 7.4-2. Summary of within-study assay validation in urine

10.4.1.6 Iloperidone in urine

Nominal conc. in QC Sample [ng/mL]	Number of Determinations	Mean Recovery [% of nominal conc.]	Precision* [%]
0.207	6	102.0	12.9
25.9	6	115.0	11.0
104	6	118.0	4.21

10.4.1.7 P88-8991 in urine

Nominal conc. in QC Sample [ng/mL]	Number of Determinations	Mean Recovery [% of nominal conc.]	Precision* [%]
0.396	6	100.0	5.77
49.5	6	105.0	3.49
198.0	6	108.0	4.04

10.4.1.8

10.4.1.9 P95-12113 in urine

Nominal conc. in QC Sample [ng/mL]	Number of determinations	Mean Recovery [% of nominal conc.]	Precision* [%]
0.800	4	107.0	3.45
100.0	4	107.0	9.81
400	4	102.0	7.30

* coefficient of variation: (100 • standard deviation/mean)

The limit of quantitation for urine analysis was 0.1 ng/mL for iloperidone, 0.2 ng/mL for P88-8991 and 0.4 ng/mL for P95-12113. For details on assay performance see Appendix 5.

10.4.1.10 Dextromethorphan and dextrorphan assay performance in serum

The calibration curves were fitted to $\ln y = a*(\ln x)^2 + b*\ln x + c$ with a coefficient of correlation higher than 0.999 for both analytes

Within-study assay validation was performed by analysis of QC samples together with the study samples. The range of quality control samples and their corresponding accuracy and precision were 0.148-17.3 ng/mL, 101-105% and 3.6-6.3% for dextromethorphan and 1.5-175.0 ng/mL, 101-104% and 4.3-5.8% for dextrorphan, respectively. The results are presented in Table 7.4-3.

Table 7.4-3. Summary of within-study assay validation in serum

10.4.1.11 Dextromethorphan in serum

Nominal conc. in QC Sample [ng/mL]	Number of Determinations	Mean Recovery [% of nominal conc.]	Precision* [%]
0.148	24	104.9	6.3
7.41	24	104.8	4.4
17.29	24	101.3	3.6

10.4.1.12 Dextrorphan in serum

Nominal conc. in QC Sample [ng/mL]	Number of Determinations	Mean Recovery [% of nominal conc.]	Precision* [%]
1.5	22	104.1	5.8
75	22	104.1	5.3
175	22	100.9	4.3

The limit of quantitation for serum analysis was 0.05 ng/mL for dextromethorphan and 0.5 ng/mL for dextrorphan. For details on assay performance see Appendix 5.

10.4.2 7.4.2. Pharmacokinetic profiles and variables

At screening, Subject 02 was genotyped as an extensive metabolizer; however inspection of PK information following dextromethorphan administration indicated that this subject could have the phenotype of a poor metabolizer. This subject was genotyped a second time with a more sensitive assay and still had an extensive metabolizer genotype, so PK parameters were analyzed including as well as excluding this subject. Since exclusion of Subject 02 resulted in no significant change of the least square estimate and confidence intervals (see Table 7.4-13, 7.4-14, 7.4-15), the mean PK parameters were calculated including this subject as an extensive metabolizer.

10.4.2.1 Extensive vs. poor CYP2D6 metabolizers

The mean concentration vs. time plots for iloperidone, P88-8991, and P95-12113 in extensive and poor metabolizers are presented in Figures 7.4-1, 7.4-2, and 7.4-3, respectively. The mean pharmacokinetic parameters are presented in Tables 7.4-4, 7.4-5, and 7.4-6 for iloperidone, P88-8991, and P95-12113, respectively. Individual plots and pharmacokinetic parameters are presented in Appendix 4.

10.4.2.2 Iloperidone Pharmacokinetics

Iloperidone was absorbed quickly with a median (range) t_{max} of 2.5 (2-3) hr in extensive metabolizers and slightly delayed in poor metabolizers to 3.0 (1-4) hr. The corresponding mean (CV) C_{max} values were 2.79 (27%) and 2.26 (13%) ng/mL, respectively. The exposure to iloperidone as measured by $AUC_{0-\infty}$ was 57% more in poor metabolizers than in extensive metabolizers. The elimination half-life was prolonged by 88% and the apparent clearance decreased by 43% in poor metabolizers. The amount of unchanged iloperidone excreted in urine was negligible (0.45% and 0.70% of the administered dose in extensive and poor metabolizers, respectively).

Figure 7.4-1. Mean plots of iloperidone in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

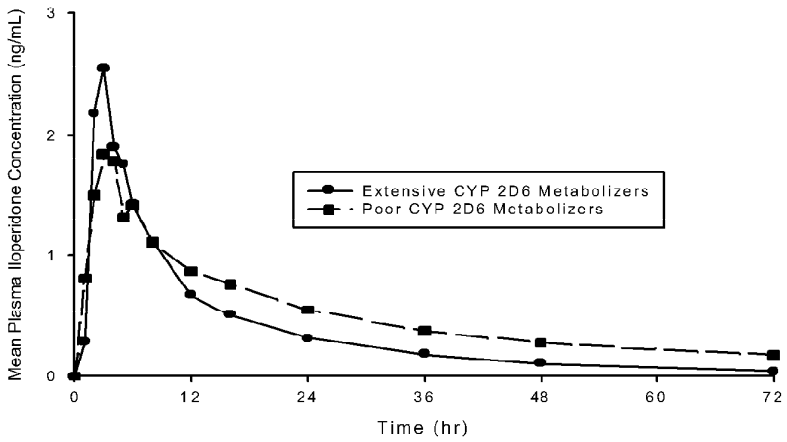

Table 7.4-4. Mean (CV%) iloperidone pharmacokinetic parameters in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

PK Parameters	Mean (CV%)		
	Extensive	Poor	% Difference**
T_{max} (hr)*	2.5 (2-3)	3 (1-4)	--
C_{max} (ng/mL)	2.79 (27)	2.26 (13)	-19.0
$AUC_{0-\infty}$ (ng*hr/mL)	29.4 (36)	46.3 (17)	57.4
$t_{½}$ (hr)	17.6 (36)	32.8 (21)	88.3
CL_T/F (L/hr)	116.5 (39)	66.4 (16)	-43.0
V_z/F (L)	2868 (49)	3095 (19)	7.9
Ae (% of dose)	0.45 (69)	0.70 (34)	35.7
CL_R (mL/min)	8.2 (56)	9.28 (25)	13.1
*Median (Range) ** % Difference = (Poor – Extensive)/Extensive X 100			

10.4.2.3 Metabolite P88-8991 Pharmacokinetics

The mean (CV) maximum concentration of P88-8991, a metabolite formed via reduction of iloperidone, was increased by 44% from 2.32 (30%) ng/mL in extensive metabolizers to 3.33 (20%) ng/mL in poor metabolizers. The $AUC_{0-\infty}$ of P88-8991 also increased by 95% in poor metabolizers (mean (CV) of 96.4 (21%) vs. 49.4 (43%) ng*hr/mL). The mean (CV%) terminal elimination half-

life was prolonged to 37.5 (20%) hrs in poor metabolizers compared to 25.5 (45%) hrs in extensive metabolizers. Although the amount of drug renally excreted as P88-8991 increased from 4.2% of administered dose in extensive metabolizers to 8.0% in poor metabolizers, the renal clearance remained about the same (46.5 mL/min and 51.3 mL/min, respectively).

Figure 7.4-2. Mean plots of metabolite P88-8991 in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

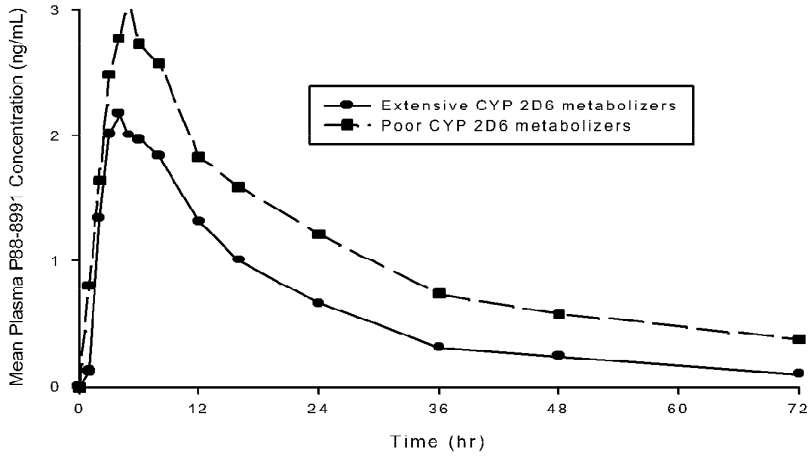

Table 7.4-5. Mean (CV%) P88-8991 pharmacokinetic parameters in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

PK Parameters	Mean (CV%)		
	Extensive	Poor	% Difference**
T_{max} (hr)*	4.0 (3-6)	4.5 (3-6)	--
C_{max} (ng/mL)	2.32 (30)	3.33 (20)	43.5
$AUC_{0-\infty}$ (ng*hr/mL)	49.4 (43)	96.4 (21)	95.1
$t_{½}$ (hr)	25.5 (45)	37.3 (20)	46.3
CL_T/f_m*F (L/hr)	68.7 (32)	32.3 (20)	-53.0
V_z/f_m*F (L)	2343 (45)	1715 (21)	-26.8
Ae (% of dose)	4.2 (57)	8.0 (30)	90.5
CL_R (mL/min)	46.5 (35)	51.3 (16)	10.3
*Median (Range) ** % Difference = (Poor – Extensive)/Extensive X 100			

10.4.2.4 Metabolite P95-12113 Pharmacokinetics

The maximum concentration of P95-12113, a metabolite formed via CYP2D6 isozyme metabolism, was decreased significantly (by 87%) in poor metabolizers (4.5 vs 0.67 ng/mL). This decrease in C_{max} was also reflected in $AUC_{0-\infty}$, which decreased by 80%. The elimination half-life was prolonged from 23 hrs in extensive metabolizers to 30.6 hrs in poor metabolizers. The amount of drug renally excreted as metabolite P95-12113 was also significantly less (76%) in poor metabolizers. In spite of this, the renal clearance of P95-12113 remained about the same in both populations (66.4 mL/min in extensive metabolizers vs 75.0 mL/min in poor metabolizers).

Figure 7.4-3. Mean plots of metabolite P95-12113 in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

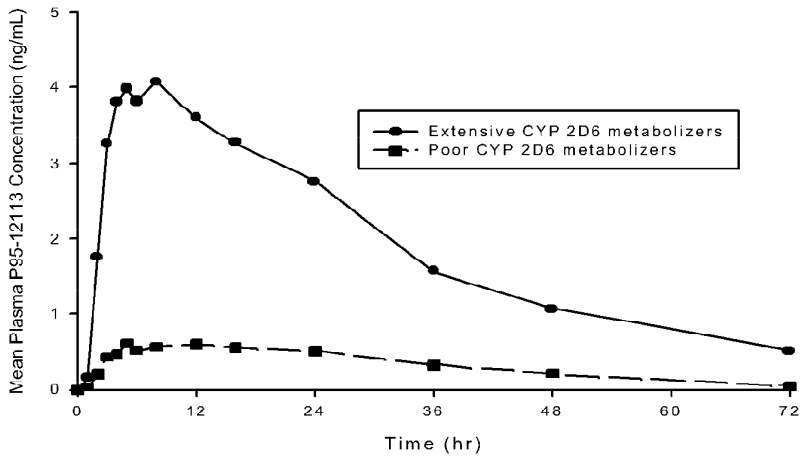

Table 7.4-6. Mean (CV%) P95-12113 pharmacokinetic parameters in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

PK Parameters	Mean (CV%)		
	Extensive	Poor	% Difference**
T_{max} (hr)*	6.0 (3-16)	8.0 (3-12)	--
C_{max} (ng/mL)	4.5 (34)	0.67 (44)	-85.0
$AUC_{0-\infty}$ (ng*hr/mL)	153.8 (26)	32.1 (36)	-79.1
$t_{½}$ (hr)	23.0 (20)	30.6 (31)	33.0
CL_T/f_m*F (L/hr)	21.5 (41)	101.4 (26)	380.9
V_z/f_m*F (L)	730.3 (53)	4520 (53)	519.1
Ae (% of dose)	19.2 (31)	4.5 (24)	-76.5
CL_R (mL/min)	66.4 (26)	75.0 (25)	12.9

*Median (Range)
** % Difference = (Poor – Extensive)/Extensive X 100

10.4.2.5 Effect of dextromethorphan on iloperidone pharmacokinetics

The mean concentration vs. time plots of iloperidone, P88-8991, and P95-12113 following administration of iloperidone alone and in combination with dextromethorphan are presented in Figures 7.4-4, 7.4-5, and 7.4-6, respectively. Mean pharmacokinetic parameters for iloperidone, P88-8991, and P95-12113 following both treatments are presented in Tables 7.4-7, 7.4-8, and 7.4-9 respectively. Individual plots and pharmacokinetic parameters are listed in Appendix 4.

10.4.2.6 Iloperidone Pharmacokinetics

The mean plasma concentration vs. time profiles of iloperidone, following administration of iloperidone alone and in combination with dextromethorphan, are superimposable and indistinguishable. The mean maximum concentration of iloperidone following administration of iloperidone alone (2.79 ng/mL) and in combination with dextromethorphan (2.75 ng/mL) appeared at the same median time of 2.5 hr. The pharmacokinetic parameters for iloperidone were similar between both treatments. The differences in C_{max}, $AUC_{0-\infty}$, $t_{½}$, CL_T/F, and V_z/F between the two treatments were less than 4.0%.

Figure 7.4-4. Mean plots of iloperidone following a 3 mg single oral dose of iloperidone administered alone and in combination with an 80 mg single oral dose of dextromethorphan HBr

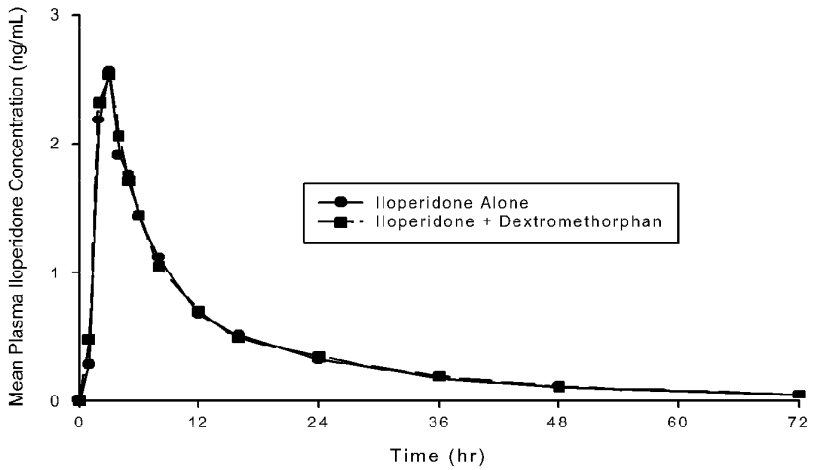

Table 7.4-7. Mean (CV%) iloperidone pharmacokinetic parameters following a 3 mg single oral dose of iloperidone administered alone and in combination with an 80 mg single oral dose of dextromethorphan HBr

PK Parameters	Mean (CV%)		
	Iloperidone alone	Iloperidone with dextromethorphan	% Difference**
T_{max} (hr)*	2.5 (2 3)	2.5 (2 4)	--
C_{max} (ng/mL)	2.79 (27)	2.75 (30)	-1.4
$AUC_{0-\infty}$ (ng*hr/mL)	29.4 (36)	30.2 (40)	2.7
$t_{½}$ (hr)	17.6 (36)	17.5 (36)	0.0
CL_T/F (L/hr)	116.5 (39)	117 (46)	0.0
V_z/F (L)	2868 (49)	2756 (42)	-3.9
Ae (% of dose)	0.45 (69)	0.51 (69)	13.3
CL_R (mL/min)	8.2 (56)	9.6 (55)	17.0

*Median (Range)
** % Difference = (ilo with dextro - ilo alone)/ilo alone X 100

10.4.2.7 Metabolite P88-8991 Pharmacokinetics

The mean plasma concentration vs. time profiles for P88-8991 following administration of iloperidone alone and in combination with dextromethorphan are also indistinguishable. The maximum concentration of the metabolite appeared in the plasma at the same time. The differences in C_{max}, $AUC_{0-\infty}$, and $t_{½}$ between the two treatments were less than 7.0%.

Figure 7.4-5. Mean plots of P88-8991 following a 3 mg single oral dose of iloperidone administered alone and in combination with an 80 mg single oral dose of dextromethorphan HBr

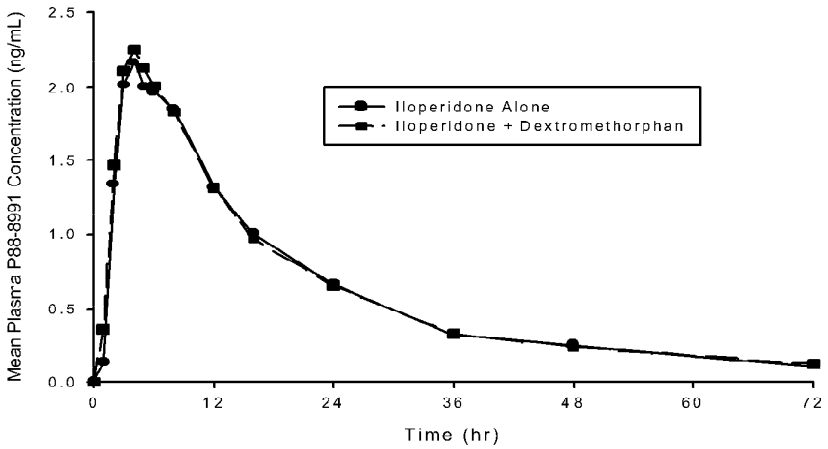

Table 7.4.-8. Mean (CV%) P88-8991 pharmacokinetic parameters following a 3 mg single oral dose of iloperidone administered alone and in combination with an 80 mg single oral dose of dextromethorphan HBr

PK Parameters	Mean (CV%)		
	Iloperidone alone	Iloperidone with dextromethorphan	% Difference**
T_{max} (hr)*	4.0 (3-6)	4.0 (2-8)	--
C_{max} (ng/mL)	2.32 (30)	2.47 (37)	6.4
$AUC_{0-\infty}$ (ng*hr/mL)	49.4 (43)	50.6 (40)	2.4
$t_{½}$ (hr)	25.5 (45)	27.0 (49)	5.9
CL_T/f_m*F (L/hr)	68.7 (32)	67.7 (37)	-1.5
V_z/f_m*F (L)	2343 (45)	2436 (50)	4.0
Ae (% of dose)	4.2 (57)	4.6 (49)	9.5
CL_R (mL/min)	46.5 (35)	51.5 (24)	9.7
*Median (Range) ** % Difference = (ilo with dextro - ilo alone)/ilo alone X 100			

10.4.2.8 Metabolite P95-12113 Pharmacokinetics

The mean plasma concentration vs. time profiles for P95-12113 following administration of iloperidone alone and in combination with dextromethorphan are also indistinguishable. The formation and clearance of the metabolite were similar between treatments. The differences in C_{max}, $AUC_{0-\infty}$, Ae, and CL_R between the two treatments were less than 6%; the difference in $t_{½}$ was about 13.0%.

Figure 7.4-6. Mean plots of P95-12113 following a 3 mg single oral dose of iloperidone administered alone and in combination with an 80 mg single oral dose of dextromethorphan HBr

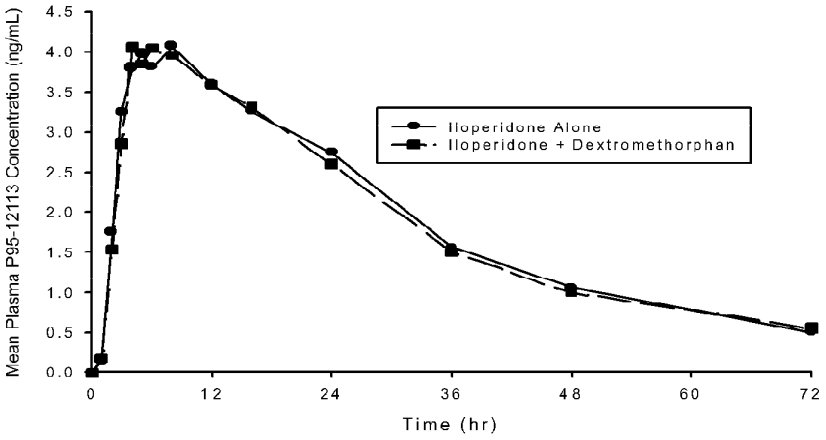

Table 7.4-9. Mean (CV%) P95-12113 pharmacokinetic parameters following a 3 mg single oral dose of iloperidone administered alone and in combination with an 80 mg single oral dose of dextromethorphan HBr

PK Parameters	Mean (CV%)		
	Iloperidone alone	Iloperidone with dextromethorphan	% Difference**
T_{max} (hr)*	6.0 (3-16)	5.0 (4-16)	--
C_{max} (ng/mL)	4.5 (34)	4.57 (35)	0.0
$AUC_{0-\infty}$ (ng*hr/mL)	153.8 (26)	155.1 (30)	0.84
$t_{½}$ (hr)	23.0 (20)	26.2 (32)	13.9
CL_T/f_m*F (L/hr)	21.5 (41)	21.4 (36)	0.0
V_z/f_m*F (L)	730.3 (53)	818 (55)	12.0
Ae (% of dose)	19.2 (31)	20.2 (29)	5.2
CL_R (mL/min)	66.4 (26)	70.0 (29)	5.4

*Median (Range)
** % Difference = (ilo with dextro - ilo alone)/ilo alone X 100

10.4.2.9 Effect of iloperidone on dextromethorphan pharmacokinetics

The mean concentration vs. time plots of dextromethorphan and dextrorphan following administration of dextromethorphan alone and in combination with iloperidone are presented in Figures 7.4-7 and 7.4-8, respectively. Mean pharmacokinetic parameters of dextromethorphan and dextrorphan

following both treatments are presented in Tables 7.4-10 and 7.4-11, respectively. Individual plots and pharmacokinetic parameters are listed in Appendix 4.

10.4.2.10 Dextromethorphan Pharmacokinetics

Dextromethorphan was absorbed quickly with a similar median t_{max} of 2 hrs following both treatments of dextromethorphan alone and in combination with iloperidone. The corresponding means (CV) of C_{max} were 7.0 (133%) and 8.68 (121%) ng/mL. Although there was a 24% difference in the mean C_{max} values, the coefficients of variation were high. The differences in $AUC_{0-\infty}$, $t_{½}$, CL_T/F, and V_Z/F were less than 10%.

Figure 7.4-7. Mean plots of dextromethorphan following an 80 mg single oral dose of dextromethorphan HBr administration alone and in combination with a 3 mg single oral dose of iloperidone

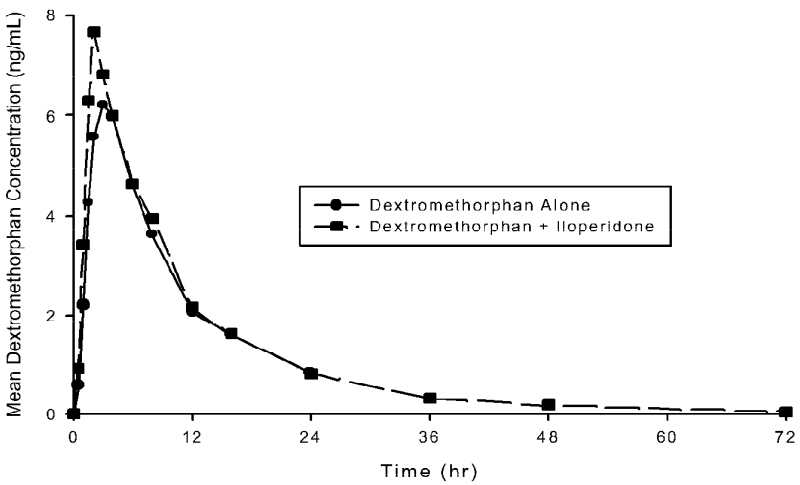

Table 7.4-10. Mean (CV%) dextromethorphan pharmacokinetic parameters following an 80 mg single oral dose of dextromethorphan HBr administration alone and in combination with a 3 mg single oral dose of iloperidone

PK Parameters	Mean (CV%)		
	Dextromethorphan alone	Dextromethorphan with iloperiodone	% Difference**
T_{max} (hr)*	2.0 (1.5-4)	2.0 (1-3)	--
C_{max} (ng/mL)	7.0 (133)	8.68 (121)	24.0
$AUC_{0-\infty}$ (ng*hr/mL)	76.0 (203)	83.3 (195)	- 9.6
$t_{½}$ (hr)	7.2 (19)	7.3 (29)	0.0
CL_T/F (L/hr)	2792 (76)	2561 (82)	-8.2
V_z/F (L)	27430 (76)	25825 (88)	-5.8
*Median (Range) ** % Difference = (Dextro with Ilo - Dextro alone)/Dextro alone X 100			

10.4.2.11 Dextrorphan pharmacokinetics

The metabolite dextrorphan, formed via CYP2D6 metabolism of dextromethorphan, was formed quickly and at the same rate with a median t_{max} of 2 hrs following both treatments of dextromethorphan alone and in combination with iloperidone. The corresponding means (CV) of C_{max} were 1049 (22%) and 996 (23%) ng/mL, respectively. The differences between the treatments for C_{max} and $AUC_{0-\infty}$ were less than 5%. However, concomitant administration of iloperidone prolonged the elimination half-life of dextrorphan by 58% (4.55 vs. 7.17 hr).

Figure 7.4-8. Mean plots of dextrorphan following an 80 mg single oral dose of dextromethorphan HBr administration alone and in combination with a 3 mg single oral dose of iloperidone

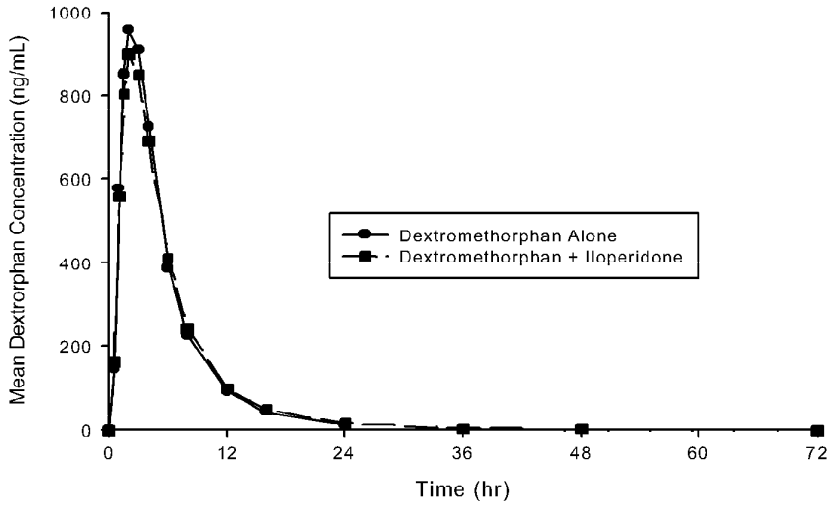

Table7.4-11. Mean (CV%) dextrorphan pharmacokinetic parameters following an 80 mg single oral dose of dextromethorphan HBr administration alone and in combination with a 3 mg single oral dose of iloperidone

PK Parameters	Mean (CV%)		
	Dextrorphan alone	Dextrorphan with iloperidone	% Difference**
T_{max} (hr)*	2.0 (1.5 4)	2.0 (1.5 4)	--
C_{max} (ng/mL)	1049 (22)	996 (23)	-5.0
$AUC_{0-\infty}$ (ng*hr/mL)	5776 (17)	5833 (19)	0.98
$t_{½}$ (hr)	4.55 (32)	7.17 (30)	57.5
CL_T/f_m*F (L/hr)	11.0 (19)	11.0 (21)	0.0
V_z/f_m*F (L)	74.3 (53)	115.3 (48)	55.2
*Median (Range) ** % Difference = (Dextro with Ilo - Dextro alone)/Dextro alone X 100			

10.4.2.12 Metabolic Ratio

The mean ratios of $AUC_{0-\infty}$ of metabolite P88-8991 to iloperidone and metabolite P95-12113 to iloperidone following administration of iloperidone alone in CYP2D6 extensive and poor

metabolizers and along with dextromethorphan in extensive metabolizers are presented in Table 7.4-12. The mean ratios of $AUC_{0-\infty}$ of dextrorphan to dextromethorphan in extensive metabolizers with and without iloperidone is also presented in Table 7.4-12. Individual ratios are given in Appendix 4.

Table 7.4-12. Mean (CV%) of ratios of metabolite to parent drug following iloperidone and dextromethorphan administration

Group	Extensive metabolizers			Poor metabolizers
Treatment	Iloperidone alone	Iloperidone + Dextromethorphan	Dextromethorphan	Iloperidone
P88/iloperidone	1.77 (33)	1.81 (34)	--	2.11 (22)
P95/iloperidone	6.19 (56)	6.25 (62)	--	0.737 (55)
Dextrorphan/Dextro-methorphan	--	250 (75)	274 (71)	--

The ratios of $AUC_{0-\infty}$ of P88-8991 to iloperidone following administration of iloperidone alone and along with dextromethorphan in extensive metabolizers were almost identical. The ratios for P95-12113 to iloperidone were also similar between treatments. This indicated that metabolism process of iloperidone was not altered by the presence of another substrate for CYP2D6 isoenzyme. As expected, the ratios for P95-12113 to iloperidone in poor metabolizers was almost 10 fold less than in extensive metabolizers. Since iloperidone metabolized via CYP2D6 isoenzyme pathway was obstructed in poor metabolizer, conversion of iloperidone to P88-8991 via reduction increased. This is indicated by higher P88-8991 to iloperidone ratio in poor metabolizers than in extensive metabolizer. However, this increase could not completely compensate for the reduction in P95-12113 formation.

The ratios of $AUC_{0-\infty}$ of dextrorphan to dextromethorphan following administration of dextromethorphan alone and in combination with iloperidone were similar indicating that metabolism of dextromethorphan to dextrorphan via CYP2D6 isoenzymes in extensive metabolizers were not altered due to the presence of iloperidone, another substrate for CYP2D6 isoenzyme. Subject 02, who was genotyped as an extensive metabolizer, had a dextrorphan to dextromethorphan $AUC_{0-\infty}$ ratio that was 25 fold less than the mean $AUC_{0-\infty}$ ratio for the rest of the extensive cohort.

10.4.3 7.4.3. Statistical results

10.4.3.1 Pharmacokinetics of iloperidone between poor and extensive CYP2D6 metabolizers

The statistical analysis results from ANOVA model are summarized in Table 7.4-13.

Table 7.4-13. Least-squares mean ratio of PK parameters from ANOVA of poor vs. extensive metabolizers

	Parameter	Least-squares mean ratio +	90% confidence interval +
Iloperidone	AUC_{0-8}	1.659	(1.306,2.107)
	AUC_{0-t}	1.474	(1.161,1.871)
	C_{max}	0.860	(0.691,1.069)
?	C_{max}	0.807	(0.695,0.938)
	CL_R	1.280	(0.878,1.867)
‡	CL_T/F	0.603	(0.475,0.765)
	Ae_{0-t}	1.599	(1.067,2.396)
P88-8991	AUC_{0-8}	2.052	(1.621,2.596)
	AUC_{0-t}	1.85	(1.482,2.308)
	C_{max}	1.476	(1.203,1.811)
	CL_R	1.166	(0.906,1.501)
	Ae_{0-t}	1.933	(1.426,2.619)
P95-12113 *	AUC_{0-8}	0.208	(0.165,0.261)
*	AUC_{0-t}	0.145	(0.104,0.202)
	C_{max}	0.147	(0.105,0.204)
	CL_R	1.131	(0.940,1.361)
*	Ae_{0-t}	0.197	(0.148,0.261)

+: The ratio of least-squares means of poor vs. extensive metabolizers and the 90% confidence interval were obtained from the analysis of logarithmically transformed data.

?: A residual outlier, contributed by Subject 103, was identified; removal of the outlier resulted in the confidence interval no longer containing 1.

‡: Since CL/f = dose/AUC_{0-8}, the least-squares mean of CL/f and its 90% confidence limits were obtained by taking the reciprocals of those of AUC_{0-8}.

*: A residual outlier, contributed by Subject 02, was identified; exclusion of the subject resulted in no significant change of the least square estimate and confidence intervals.

In general for both iloperidone and P88-8991, subjects genotyped as poor metabolizers had an AUC_{0-8}, AUC_{0-t}, and C_{max} more than 1.5 times greater than the extensive metabolizers. The only exception was C_{max} for iloperidone, which was less in poor metabolizers.

However, for P95-12113 much less exposure in terms of AUC_{0-8}, AUC_{0-t}, and C_{max} was observed in poor metabolizers. The difference between the two cohorts was highly significant.

The renal clearances were similar in all cases between the two cohorts. Wilcoxon's rank sum test showed no significant difference in t_{max} between the two cohorts.

10.4.3.2 Effect of dextromethorphan on the pharmacokinetics of iloperidone

The analysis results from ANOVA are summarized in the Table 7.4-14.

Table 7.4-14. Least-squares mean ratio of PK parameters (AUC_{0-8}, AUC_{0-t}, C_{max}, CL_R, CL_T/F, and Ae_{0-t}) from ANOVA of iloperidone + dextromethorphan vs. iloperidone alone

	Parameter	Least-squares mean ratio +	90% confidence interval +
Iloperidone	AUC_{0-8}	1.013	(0.958,1.071)
	AUC_{0-t}	1.015	(0.962,1.071)
	C_{max}	1.006	(0.911,1.112)
	CL_R	1.198	(0.972,1.478)
‡	CL_T/F	0.987	(0.935,1.043)
	Ae_{0-t}	1.133	(0.940,1.366)
P88-8991	AUC_{0-8}	1.025	(0.968,1.085)
	AUC_{0-t}	1.013	(0.955,1.073)
	C_{max}	1.056	(0.985,1.132)
*	CL_R	1.151	(0.993,1.335)
	Ae_{0-t}	1.119	(0.976,1.284)
P95-12113	AUC_{0-8}	1.005	(0.961,1.050)
	AUC_{0-t}	0.987	(0.939,1.037)
	C_{max}	1.015	(0.960,1.073)
	CL_R	1.044	(0.969,1.124)
	Ae_{0-t}	1.030	(0.965,1.099)

+: The ratio of least-squares means and the 90% confidence interval were obtained from the analysis of logarithmically transformed data.

‡: Since CL_T/F = dose/AUC_{0-8}, the least-squares mean of CL_T/F and its 90% confidence limits were obtained by taking the reciprocals of those of AUC_{0-8}.

*: A residual outlier, contributed by Subject 05, was identified; exclusion of the subject resulted in no significant change of the least square estimate and confidence intervals.

In general, the mean PK parameters AUC_{0-8}, AUC_{0-t}, and C_{max} were not altered when dextromethorphan was co-administered. The 90% confidence intervals of AUC_{0-8}, AUC_{0-t}, and C_{max} all fell within the conventional "no effect" boundaries of 80-125%.

About 10% more iloperidone and its metabolite P88-8991 were renally excreted when dextromethorphan was co-administered with iloperidone compared to iloperidone alone; however this change was not significant. Wilcoxon's signed rank test for paired differences of t_{max} between the two treatments (iloperidone in combination with dextromethorphan vs. iloperidone alone) revealed no significant difference for both iloperidone and its metabolites (P88-8991 and P95-12113).

10.4.3.3 Effect of iloperidone on the pharmacokinetics of dextromethorphan

The analysis results from ANOVA were summarized in the Table 7.4-15.

Table 7.4-15. Least-squares mean ratio of PK parameters (AUC_{0-8}, AUC_{0-t}, C_{max}, and CL_T/F) from ANOVA of iloperidone + dextromethorphan vs. dextromethorphan alone

		Parameter	Least-squares mean ratio [+]	90% confidence interval [+]
Dextromethorphan		AUC_{0-8}	1.123	(1.008,1.251)
		AUC_{0-t}	1.171	(1.045,1.311)
		C_{max}	1.264	(1.053,1.517)
	‡	CL_T/F	0.891	(0.800,0.992)
Dextrorphan		AUC_{0-8}	1.007	(0.980,1.034)
		AUC_{0-t}	1.027	(0.995,1.060)
	*	C_{max}	0.945	(0.910,0.980)

[+]: The ratio of least-squares means and the 90% confidence interval were obtained from the analysis of logarithmically transformed data.

‡: Since CL_T/F = dose/AUC_{0-8}, the least-squares mean of CL_T/F and its 90% confidence limits were obtained by taking the reciprocals of those of AUC_{0-8}.

*: A residual outlier, contributed by Subject 02, was identified; exclusion of the subject resulted in no significant change of the least square estimate and confidence intervals.

The exposure (AUC_{0-8} and AUC_{0-t}) of dextromethorphan was significantly increased in subjects when iloperidone was co-administered. However, for dextrorphan there were no significant changes in AUC_{0-8} and AUC_{0-t} between the two treatments.

The peak concentration was higher for dextromethorphan yet lower for dextrorphan in subjects with iloperidone co-administered.

Neither sequence nor period effect was found to be significant. Wilcoxon's signed rank test showed that t_{max} for dextromethorphan was reached earlier in subjects to whom iloperidone was co-administered than those given dextromethorphan alone. For dextrorphan, no difference in t_{max} between the two treatments was found.

11 8. Discussion

Iloperidone is extensively metabolized by the liver with only about 0.5% of unchanged iloperidone eliminated via renal excretion. *In vitro* human liver microsome data and *in vivo* human ADME data identified three major pathways for metabolism of iloperidone: reduction, hydroxylation (mediated by CYP2D6), and *O*-demethylation (mediated by CYP3A4). In an earlier human study, the main component in plasma was found to be the reduced metabolite P88-8991, which had an AUC 70-90% greater than that of the parent compound. The P89-9124 metabolite, resulting from *O*-demethylation via CYP3A4, was only a minor plasma component. The CYP2D6 pathway may play an important role in the metabolism of iloperidone because the α-hydroxy ketone metabolite, P94-11840, undergoes further oxidation and decarboxylation via CYP2D6 to P95-12113. P95-12113 has plasma concentrations 2-5 fold greater than iloperidone, but has less affinity for D_2, $5HT_2$, and $alpha_1$-receptors, so it is considered pharmacologically inactive. Since CYP2D6 isozyme is polymorphic, with approximately 7-10% of the Caucasian population categorized as poor metabolizers, this study was conducted to evaluate whether there was a difference in the metabolism

and excretion of iloperidone between subjects genotyped as CYP2D6 extensive and poor metabolizers. In addition, the potential for drug-drug interactions was explored by using dextromethorphan hydrobromide as a CYP2D6 prototype substrate.

Exposure to iloperidone was significantly higher (57%) in poor metabolizers with a 90% confidence interval of 130-210%. The increase in exposure was also associated with increase in half-life by 88% and decrease in the apparent clearance by 43%. On the other hand, the exposure, maximum concentration, and renal excretion of P95-12113 decreased by 79%, 85%, and 76%, respectively, in poor metabolizers. This was consistent with what was expected in this population.

Approximately 23.85% of the iloperidone dose was renally excreted in extensive metabolizers as either parent drug, P88-8991, or P95-12113, whereas, only 13.2% of drug was renally excreted in poor metabolizers. This is a 45% reduction of renal excretion as parent drug or metabolites. Since iloperidone is also metabolized to other metabolites, it is likely that formation of these metabolites may have increased to compensate for the complete elimination of iloperidone.

The renal clearance of P95-12113 was similar in both populations. This may be due to the fact that polymorphic impairment in metabolism in poor metabolizers only affected the formation of P95-12113 but not its elimination. The elimination of P95-12113 mainly occurred via renal excretion without further metabolism.

Since the metabolite P88-8991 is formed by reduction of iloperidone via reductase enzymes, it is unlikely that the polymorphically impaired 2D6-enzyme metabolism capacity in poor metabolizers will affect the metabolism and/or excretion of P88-8991. In spite of this fact, C_{max} and $AUC_{0-\infty}$ of P88-8991 in poor metabolizers were increased by 43% and 95%, respectively, in comparison with extensive metabolizers. The amount of unchanged P88-8991 in urine was also increased by 2-fold in poor metabolizers. A logical explanation of such phenomenon is that in order to compensate for the reduced formation of P95-12113 more iloperidone was metabolized to P88-8991 in poor metabolizers. However, The formation of metabolite P88-8991 could not fully compensate the lack of formation of P95-12113, so iloperidone concentrations were also increased in poor metabolizers as mentioned earlier.

Even though the exposure of iloperidone and its active metabolite are higher in poor CYP2D6 metabolizers, the frequency of adverse events reported was not significantly different than those reported by extensive CYP2D6 metabolizers, when iloperidone was given alone. However, the number of AEs per extensive metabolizer was double that of the poor metabolizers. Clinically there does not appear to be a safety concern in either of the 2 groups.

Though pharmacokinetic properties of iloperidone were significantly altered in poor CYP2D6 metabolizers, concomitant administration of dextromethorphan, a CYP2D6 substrate, did not change the pharmacokinetic properties of iloperidone or its metabolites. The plasma concentration vs. time curves for iloperidone, P88-8991, and P95-12113 following iloperidone alone and combination treatment with dextromethorphan were essentially identical. The 90% confidence intervals for $AUC_{0-\infty}$ and C_{max} of iloperidone were 96-107% and 91-111%, respectively. Concomitant administration of iloperidone altered the pharmacokinetic properties of dextromethorphan only to a small degree,

unlikely to be of clinical relevance. The 90% confidence interval for $AUC_{0-\infty}$ of dextromethorphan was 101-125%. This may indicate that iloperidone is not likely to interfere with the metabolism and excretion of other drugs which are primarily metabolized via CYP2D6.

Within Cohort 1 (EM), the number of AEs reported after taking iloperidone with dextromethorphan was less than after taking iloperidone alone. Subjects in Cohort 1 were all exposed to iloperidone alone first in Period 1 and then randomized to the other 2 treatments. Usually the first exposure to iloperidone elicits more AEs than a second or third exposure, even after a washout period. Only one adverse event was reported after taking dextromethorphan alone.

Overall, the 3 mg iloperidone dose was well tolerated by healthy volunteers, whether given to poor or extensive CYP2D6 metabolizers, or when administered alone or in combination with dextromethorphan.

12 9. Conclusions

- Exposure to iloperidone and P88-8991 was significantly increased, while exposure to P95-12113 was significantly decreased in poor CYP2D6 metabolizers compared to extensive CYP2D6 metabolizers.
- Poor and extensive CYP2D6 metabolizers tolerated the drug similarly and there were no safety concerns indicated in either population.
- In extensive metabolizers, dextromethorphan did not alter the metabolism of iloperidone; changes in dextromethorphan pharmacokinetics when a 3 mg dose of iloperidone was coadministered appeared to be too small to be of clinical relevance. Thus, an interaction between iloperidone and other CYP2D6 substrates is unlikely.
- Iloperidone and dextromethorphan were tolerated when given together or alone, with no lasting clinically significant findings in the safety assessments.

13 10. Reference list

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14 11. Post-text Tables

Table 11.1-1. Evaluation study schedule

Evaluation	Screening	Baseline	Pre-Dose	Hours Post Dose															End-of-Study
	Days -21 to -2	Day-1	0-hour	0.50	1	1.5	2	3	4	5	6	8	12	16	24	36	48	72	
1 Inclusion /Exclusion Criteria	X	X[2]																	
2 Past Med Hx/Curr Med Cond	X	X[2]																	
3 Physical Examination	X	X																	X
4 Laboratory Safety Tests	X	X																	X
5 ECG	X	X																	X
6 Vital Signs Dextromethorphan only	X[1]	X[1]	X[1]						X						X[1]				X[1]
6 Vital Signs: ILO alone or w/ Dextro	X[1]	X[1]	X[1]		X		X		X		X	X	X[1]		X[1]		X[1]	X[1]	X[1]
7 Body Temperature	X	X																	X
8 Body Weight	X	X																	X
9 Serology (Hepatitis/HIV)	X																		
10 Genotyping- 2D6 metabolizer	X3																		
11 Urine Cotinine	X	X																	
12 Pregnancy Test	X	X																	X
13 Concomitant Meds/Therapies	X	X	As required																X
14 Drug Screen	X	X																	
15 Pk Sampling Iloperidone (only)			X		X		X	X	X	X	X	X	X	X	X	X	X	X	
16 PK Sampling Dextomethorphan			X	X	X	X	X	X	X		X	X	X	X	X				
17 PK Sampling Iloperidone & Dextro			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
18 Urine Collection			X									X		X	X		X		
19 Comments	As required																		X
20 Adverse Events			As required																X
20 Study Completion																			X

1 Standing and supine blood pressure and pulse measurements required. All others will be supine 2 Review of Inclusion and Exclusion criteria is required at baseline evaluation
3 If previously genotyped, laboratory results must be available