- The RB values were independent of OPC-14597 blood concentrations.
- These data suggested that distribution of OPC-14597 into blood cells in these animals and humans was not high, and there was no accumulation of OPC-14597 in blood cells.

Report-013353: ***The Blood-Plasma Partition Ratio of OPC-14597 in Cynomolgus Monkeys***

Table 1. The Blood-Plasma Partition Ratio (R_B) of OPC-14597 in Fasting Monkey (n=3)

OPC-14597 C (ng/ml)	20	200	2000
RB of OPC-14597	0.85±0.10	0.81±0.04	0.85±0.05

Study 178/337039/006: ***Tissue Distribution of Total Radioactivity following Oral Administration of [14C]-BMS-337039 to Male and Female Sprague-Dawley Rats***

Table 1. Mean Tissue:Plasma Concentration Ratios After Administration of a Single Oral Dose of [^{14}C]-BMS-337039 (10 mg/kg) to Male Sprague-Dawley Rats

Matrix	0.5 h	2 h	4 h	8 h	24 h	48 h
Adrenal glands	2.25±0.84	12.7±4.5	18.0±4.8	26.6±6.1	110±71	275
Aorta	0.43±0.13	1.36±0.37	1.78±0.08	0.97±0.13	1.52	NA
Bladder (urinary)	0.71±0.39	2.11±0.31	2.78±1.34	1.42±0.31	1.01±0.10	NA
Blood	0.62±0.03	0.69±0.01	0.71±0.02	0.64±0.03	0.74±0.11	NA
Cerebellum	0.16	0.49±0.13	0.64±0.13	0.51	NA	NA
CSF	NA					
Cerebrum	0.12±0.03	0.52±0.15	0.69±0.17	0.42±0.09	0.73±0.40	NA
Epididymis	0.18±0.04	1.02±0.36	2.60±0.54	2.30±0.20	2.69±1.45	5.73
Eyes (both)	0.15	0.48±0.14	0.55±0.09	0.58	NA	NA
Kidneys	5.62±1.94	8.03±0.24	8.46±1.45	8.28±1.47	11.7±3.1	18.1
Liver	46.2±14.3	53.7±3.5	42.8±7.6	41.9±8.4	44.5±17.8	88.0
Lungs	2.59±0.94	8.37±0.91	9.81±1.85	5.10±0.55	4.52±2.02	6.53
Medulla oblongata	0.13±0.02	0.64±0.20	0.92±0.22	0.63±1.1	1.16±0.53	2.31
Prostate	0.35±0.20	1.75±0.93	4.78±1.23	2.72±1.09	5.37±1.42	14.8
Sublingual glands	0.46±0.18	3.05±1.04	4.55±0.57	3.95±0.87	21.6±25.1	NA
Testes	0.11±0.03	0.80±0.37	2.27±0.65	2.47±0.20	4.40±1.87	14.0

Table 2. Mean Tissue:Plasma Concentration Ratios After Administration of a Single Oral Dose of [^{14}C]-BMS-337039 (10 mg/kg) to Female Sprague-Dawley Rats

Matrix	0.5 h	2 h	4 h	8 h	24 h	48 h
Adrenal glands	5.42±2.29	16.3±4.6	24.7±3.0	24.5±2.1	166±5	NA
Aorta	0.83±0.28	1.75±0.67	2.24±0.35	1.74±0.13	2.54	NA
Bladder (urinary)	0.78±0.30	2.49±0.78	5.09±2.83	2.51±0.64	1.01±0.10	NA
Blood	0.57±0.05	0.66±0.05	0.70±0.04	0.61±0.05	0.74±0.11	NA
Bone (femur)	0.43±0.15	1.42±0.30	1.78±0.34	1.30±0.14	0.74±0.11	NA
Bone marrow	1.09±0.43	4.02±1.42	6.14±0.43	3.56±0.35	0.74±0.11	NA
Cerebellum	0.27±0.11	0.58±0.14	0.91±0.24	0.38	NA	NA
CSF	NA					

Table 2. Mean Tissue:Plasma Concentration Ratios After Administration of a Single Oral Dose of [^{14}C]-BMS-337039 (10 mg/kg) to Female Sprague-Dawley Rats

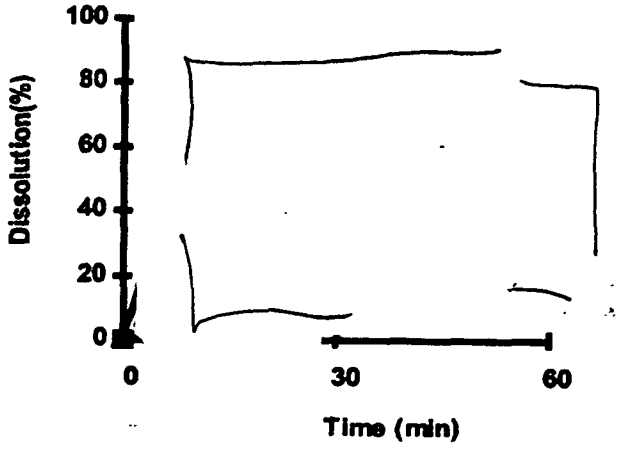
Matrix	0.5 h	2 h	4 h	8 h	24 h	48 h
Cerebrum	0.26±0.13	0.68±0.34	1.13±0.42	0.56±0.07	0.73±0.40	NA
Eyes (both)	0.19±0.03	0.51±0.08	0.76±0.07	0.69±0.07	NA	NA
Fat (brown)	0.44±0.12	1.87±0.86	1.85±0.38	0.97±0.29	NA	NA
Fat (reproductive)	0.41±0.17	2.56±0.96	5.70±2.07	3.72±1.22	NA	NA
Harderian glands	1.15±0.39	9.61±3.25	33.8±9.4	58.6±13.4	NA	NA
Heart	1.21±0.55	2.48±0.51	3.42±0.57	1.76±0.07	NA	NA
Kidneys	4.93±0.97	7.19±1.04	8.07±2.33	6.37±0.66	11.7±3.1	18.1
Large intestine	1.46±0.10	3.55±0.93	19.4±18.1	205±85	NA	NA
Liver	37.3±5.7	39.1±10.7	27.0±7.6	35.3±8.9	44.5±17.8	88.0
Lungs	4.18±1.62	15.5±6.7	17.9±5.1	7.7±1.5	4.52±2.02	6.53
Lymph nodes	2.22±0.83	6.97±1.53	8.59±0.52	5.45±0.52	NA	NA
Medulla oblongata	0.31±0.18	1.03±0.30	1.83±0.45	0.90±0.02	1.16±0.53	2.31
Muscle (thigh)	0.32±0.12	1.32±0.38	2.56±0.48	1.31±0.11	5.37±1.42	14.8
Ovaries	2.16±0.77	7.86±2.25	11.5±0.9	9.80±1.38	NA	NA
Pancreas	5.57±2.49	15.3±3.9	21.5±4.8	22.1±1.9	63.9±8.4	NA
Pituitary	0.98±0.16	5.64±1.47	7.6±1.5	8.1±1.7	32.0±5.6	NA
Skin	0.49±0.19	1.49±0.41	2.58±0.47	1.75±0.11	3.90±0.21	NA
Small intestine	108±19	160±58	211±16	64.6±16.5	37.4±4.9	NA
Spleen	1.94±1.00	4.92±1.61	6.95±0.87	3.83±0.34	6.64±0.55	NA
Stomach	490±371	65.5±36.6	23.7±12.4	4.30±0.81	7.15±2.12	NA
Sublingual glands	0.66±0.24	4.20±1.53	7.11±1.26	8.64±2.45	199±146	NA
Submaxillary glands	1.47±0.99	7.94±2.28	19.5±5.2	43.5±5.5	266±62	NA
Thymus	0.62±0.26	3.21±1.01	6.30±1.11	3.50±0.23	6.64±NA	NA
Thyroid/parathyroid	0.96±0.11	3.39±0.96	5.60±0.88	4.30±0.46	14.5±NA	NA
Trachea	0.54±0.08	1.55±0.63	3.27±0.91	20.2±28.9	7.73±0.60	NA
Uterus	0.75±0.28	2.89±0.80	5.82±0.78	4.24±0.62	NA	NA

Dissolution Method Development and Dissolution Data
Vol. 1.4: Validation of the Dissolution Method (pH 1.2) for Aripiprazole

Formulation Development History
Aripiprazole tablets in strengths of 0.5-, 1-, 5-, 10- and 15-mg have been used in clinical investigations. All of the tablet compositions are essentially proportionally similar; i.e., the total tablet weight is the same, with the only changes being the amount of aripiprazole and a corresponding adjustment in the amount of lactose monohydrate. All of the clinical tablets are identical in appearance , was chosen over the method because the latter method showed slower dissolution rates than the former method. The was used to produce all tablets used in clinical studies and is proposed for manufacture of the tablets in this application.

For NDA registration, 2-, 5-, 10-, 15-, 20-, and 30-mg tablets are proposed for marketing. The 2-, 5-, 10- and 15-mg tablets are designed based on their corresponding clinical formulations, with a minor change in shape and addition of colorants for aesthetic and commercial purposes. The formulations of the 20- and 30-mg tablets were originally developed to be basically proportionally similar to the 15-mg tablet. However, the original 20- and 30-mg tablets exhibited less than complete and slower dissolution than other aripiprazole tablet strengths in pH 1.2 medium.

Figure 1. Dissolution profiles of 15-mg (square), original 20-mg (circle), and original 30-mg (triangle) trade tablets at pH 1.2/60 rpm



To improve the dissolution at pH 1.2, the 20- and 30-mg tablets have been re-designed to be proportionally similar to the 10-mg tablets. As a result, the dissolution of the current 20- and 30-mg tablets at pH 1.2 is markedly improved.

Figure 2. Dissolution profiles of 15-mg (square), current 20-mg (circle), and current 30-mg (triangle) trade tablets at pH 1.2/60 rpm

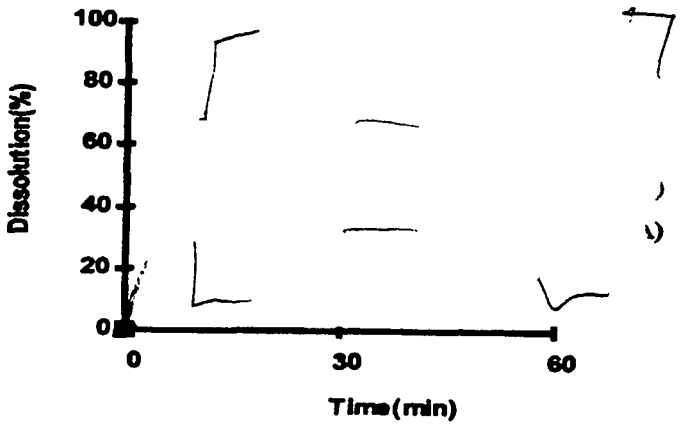


Table 1. Formulas of Aripiprazole 2-, 5-, 10-, 15-, Original 20- and 30-mg Tablets (mg with %w/w)

Ingredient	2-mg	5-mg	10-mg	15-mg	20-mg	30-mg
Aripiprazole	2.0 (2.11)	5.0 (5.26)	10.0 (10.53)	15.0 (15.79)	20.0 (15.79)	30.0 (15.79)
Lactose monohydrate						
Starch (Corn) (NF)						
Microcrystalline cellulose						
Hydroxypropyl cellulose						
Magnesium Stearate						
Coloring agent						
Total						
Tablet color	Green	Blue	Pink	Yellow	Red	White
Shape	Rectangular	Rectangular	Rectangular	Round	Round	Round

Table 2. Formulas of Aripiprazole 10-mg, Current 20-mg and 30-mg Tablets

Ingredient	Function	10-mg	20-mg	30-mg
Aripiprazole (NC)	Active Ingredient	10.0 (10.53)	20.0 (10.54)	30.0 (10.53)
Lactose monohydrate (NF)	Diluent			
Starch (Corn) (NF)	Diluent			
Microcrystalline cellulose (NF)	Diluent			
Hydroxypropyl cellulose (NF)	Binder			
Magnesium Stearate (NF)	Lubricant			
Coloring agent				
Total weight (mg)				
Tablet color		Pink, rectangular	White, round	Pink, round

Of these six tablet strengths, 5-, 10- and 15-mg tablets have been used in clinical trials in the U.S. The 2-, 5-, 10- and the 15-mg tablets are essentially proportionally similar; i.e., the total tablet weight is the same with the only change being the amount of drug with a corresponding change in the amount of lactose and the presence of a different colorant in the range of 0.02% to 0.21% w/w. The 10-, 20- and 30-mg tablets are proportionally similar; i.e., all the ingredients are in the same proportion between the three strengths except for the colorant, which is in the range of 0% to 0.02% w/w. The percentage of the other ingredients (microcrystalline cellulose, corn starch, hydroxypropyl cellulose and magnesium stearate) are identical across the entire range of the tablet strengths from 2-

mg to 30-mg. The differences in composition, when comparing the 5-, 10- and 15-mg trade and clinical tablet formulations, are considered minor.

Dissolution method and Specifications

Dissolution methods used were:

(1) Apparatus II (paddles) at 50 rpm, 900 ml of [redacted]

(2) Apparatus II (paddles) at 50 rpm, 900 ml of USP Buffer (pH 1,2)

(3) Apparatus II (paddles) at 50 rpm, 900 ml of USP Buffer (pH 6.8)

Because the low solubility of aripiprazole in pH >5, [redacted] of the drug released in the pH 6.8 dissolution medium. The solubility of aripiprazole reaches the highest at pH 4.0, therefore, [redacted] was observed for all tablet strengths. The sponsor proposed this medium as NDA method. The supportive evidence is that when aripiprazole tablets are stored under conditions of high temperature and high humidity, aripiprazole anhydrous form is converted to the monohydrate form over time and increased level of monohydrate showed a decrease in dissolution rate in this dissolution medium. However, this medium is considered nondiscriminative by OCPB reviewer and gastric pH is recommended for aripiprazole dissolution test. In gastric pH, the original 20- and 30-mg tablets showed slower dissolution, which is likely to be due to higher drug concentration [redacted], in these tablets. The higher surface concentration of aripiprazole in these tablets, facilitates rapid formation of an insoluble sticky layer/HCl salt on the surface of disintegrating particles, that inhibits dissolution of drug. To enhance dissolution of the original 20- and 30-mg tablets, a direct scale-up of 10-mg tablet [redacted] drug concentration) was used and the dissolution of the current 20- and 30-mg tablets at pH 1.2 is markedly improved. Due to limit solubility at pH 1.2 medium, the paddle speed, it is necessary to increase paddle speed from 50 rpm to [redacted] to reach [redacted] drug release in 30 minutes.

Figure 1. Dissolution Profiles of 2-, 5-, 10-, 15-, 20- and 30-mg Trade Tablets at pH 1.2/60 rpm

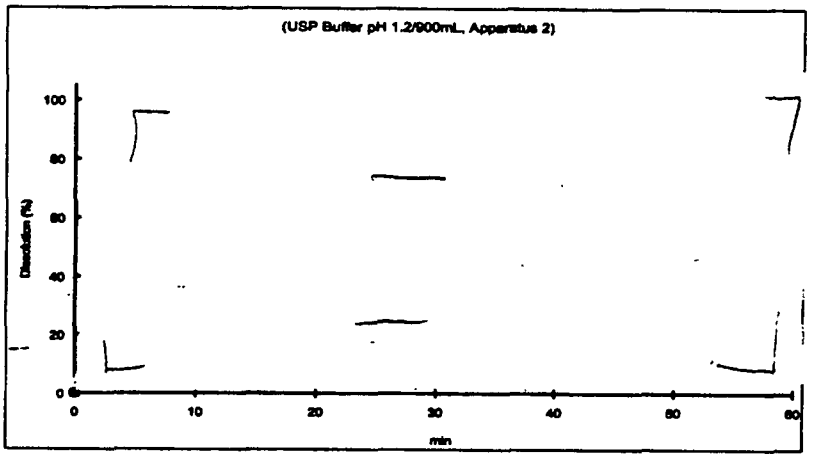
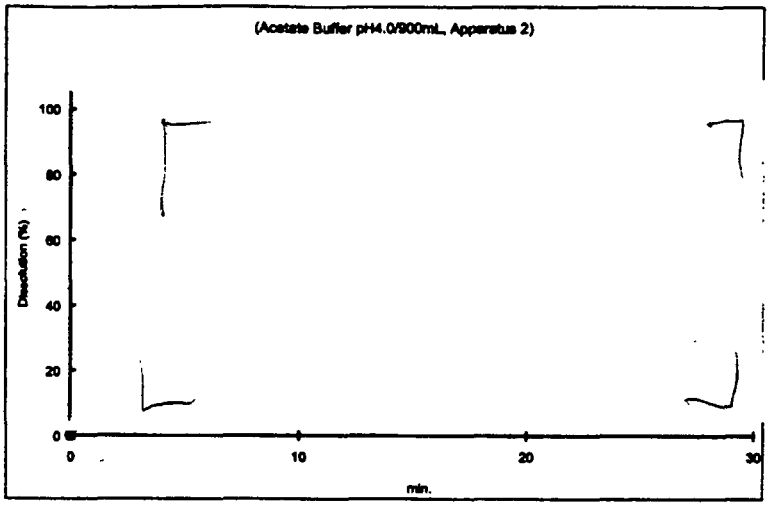


Figure 2. Dissolution Profiles of 2-, 5-, 10-, 15-, 20- and 30-mg Trade Tablets at pH 4.0/50 rpm



Assay Validation Report

A list of validated assay procedures used for analyzing plasma, urine and protein binding samples for each clinical study is provided in the NDA. The ~~~~ method was used for determination of aripiprazole, OPC-14857, OPC-3373, DM-1451, and DCPP plasma or urine concentrations following . The low limit of quantitation (LLOQ) for all compounds was ~~~~ All methods were fully validated in accordance with FDA Bioanalytical Validation Guidelines and regulatory requirements. They are acceptable.

APPEARS THIS WAY
ON ORIGINAL

Office of Clinical Pharmacology and Biopharmaceutics
PHARMACOMETRICS REVIEW

Type of Submission: New Drug Application (NME)

Submission (letter date):

Letter Date	Doc. Type	Seq. No.	Mod. Type
31-Oct-01	N	0	
17-Jan-02	N	0	BB
13-Mar-02	N	0	C
20-Mar-02	N	0	BB
29-Mar-02	N	0	BB
4-Apr-02	N	0	BB
9-May-02	N	0	BB

Brand name: ABILITAT™ (aripiprazole) Tablets

Generic name: aripiprazole

Type of dosage form and strength(s):

Indication(s): The Applicant seeks the following language: "ABILITAT is indicated for the treatment of schizophrenia."

Applicant name: Otsuka Pharmaceutical Co., Ltd., LP

OCPB and ORM Division names: Division of Pharmaceutical Evaluation 1 and Division of Neuropharmacological Drug Products

Type of Submission: Population PK and population PK/PD analyses, the PD variables are QT interval and PANSS score

OCPB Reviewer(s) and Team Leader names: Gene Williams, Ph.D. and Jogarao Gobburu, Ph.D.

Table of Contents

Table of Contents, continued

page #

1.0 Introduction

The Applicant's introduction and objectives provide an introduction to aripiprazole and the current population analysis and will be reproduced below.

There was no pre-specified population analysis plan.

1.0 Introduction, continued

The below is reproduced from Volume 1.84 p. 20 of the NDA.

1 INTRODUCTION

OPC-14597 (aripiprazole), a quinolinone derivative, is being developed as a novel antipsychotic agent. It has a mode of action that differs from those of typical and atypical antipsychotic drugs. Biochemically, OPC-14597 has been shown to be a partial agonist at members of the D_2 family of dopamine (DA) receptors. In vitro, OPC-14597 exhibits a D_2 partial agonist profile in the inhibition of prolactin release from primary cultured anterior pituitary cells. In vivo, OPC-14597 has been shown to exhibit antagonist properties in animal models of dopaminergic hyperactivity (blockade of apomorphine-induced stereotypy) and agonist activity in an animal model of dopaminergic hypoactivity (blockade of increased dopamine synthesis in reserpine-treated rats). OPC-14597 blocks post-synaptic D_2 receptors at a dose comparable to that at which it acts as an agonist at presynaptic DA autoreceptors [1].

In a study [2] to examine the pharmacokinetics of aripiprazole following multiple dosing, four parallel groups of normal volunteers received 5 mg, 10 mg, 15 mg and 20 mg qd for 14 days respectively. The results indicated that the plasma concentrations of aripiprazole on Day 14 peaked between 3-5 hours (T_{max}) with a mean (SD) peak plasma concentration (C_{max}) of 77 (19) ng/mL and 302 (173) ng/mL for the 5 mg and 20 mg doses, respectively. Steady state appeared to be attained by Day 14. The mean (SD) apparent terminal half-life ($T_{1/2}$) on Day 14 ranged from 48 (4) hours to 68 (3) hours across the doses. Another study [3] conducted in normal subjects showed that a 30 mg dose of OPC-14597 (10 mg/day for 2 days, 20 mg/day for 2 days, 30 mg/day for 10 days) had a mean (SD) C_{max} on Day 14 of approximately 450 (132) ng/mL, occurring at a median T_{max} of 3 hours with a mean (SD) terminal elimination half-life of approximately 60 (24) hours. The pharmacokinetics of OPC-14597 were linear across a dose range of 2 mg to 30 mg.

2 OBJECTIVES

This report describes a population analysis of the pharmacokinetic, pharmacodynamic, and safety data collected in trials 31-93-202, 31-94-202, 31-97-201, 31-97-202, and 31-97-203 in patients with schizophrenia [4-8].

2.1 PHARMACOKINETIC ANALYSIS

The objectives of the population pharmacokinetic (PK) modeling of aripiprazole were:

1. To describe the pharmacokinetics of aripiprazole in patients with schizophrenia.
2. To identify predictors of exposure to the drug (demographics, laboratory values, concomitant medications, disease, etc.) and identify sub-populations with altered PK.
3. To estimate the inter-individual and residual variability of aripiprazole pharmacokinetics.

2.2 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The objectives of the population pharmacokinetic/pharmacodynamic (PK/PD) modeling of aripiprazole were:

1. To assess the relationship between pharmacodynamics (as measured by a decrease from baseline in the total PANSS score) versus systemic exposure, duration of treatment and covariates.
2. To estimate the inter-individual variability of aripiprazole pharmacodynamics.

1.0 Introduction, continued

The below is reproduced from Volume 1.84 p. 21 of the NDA.

> **2.3 PHARMACOKINETIC/SAFETY ANALYSIS**
> **The objectives of the population pharmacokinetic/safety modeling of aripiprazole were to assess the relationship between patients' aripiprazole plasma concentrations and QTc prolongation.**

2.0 Reviewer's Objectives

Consistent with the Applicant not having a pre-specified analysis plan, the analysis will be considered exploratory.

The Reviewer's primary objective is to determine if age, gender, race or smoking status alter pharmcokinetics. These covariates are selected because statements regarding them appear in the package insert.

The Reviewer's secondary objective is to determine if aripirazole alters QT-interval and, if it does, if the alteration is a function of aripiprazole dose. This objective is included because of the importance, from a safety persepective, of QT-interval changes.

The determination of the relationship of aripiprazole dose or concentration to effectiveness (PANSS score) is an objective. However, the Reviewer is aware of no current regulatory decisions that will result from the determination of the relationship of aripiprazole concentration to PANSS score.

3.0 Applicant's Analysis
3.1 Design of Studies and Data Collection

Data is for one moiety: aripiprazole.

3.1 Design of Studies and Data Collection, continued

The below is reproduced from Volume 1.84 p. 60 of the NDA.

ST-1 Studies included in the population analysis

Study Number	Design/Duration of Dosing	Number and timing of PK samples	PANSS and ECG assessments
31-97-201 A phase III double-blind placebo-controlled study of aripiprazole in the treatment of psychosis	Multicenter 4-week study, 414 hospitalized patients in acute relapse with diagnosis of schizophrenia or schizoaffective disoder, with a history of responding to neuroleptics. After a 5-day placebo washout patients were randomized to one of four oral treatment arms administered once daily after breakfast: 15 or 30 mg aripiprazole, 10 mg haloperidol, or placebo. Doses were fixed and could not be modified during the study.	2 samples per patient were scheduled, at Day 14 and Day 28 (or at termination if early). In addition, samples had to be drawn upon returning to the clinic after being out on pass.	PANSS: At screening, baseline, and at the end of each week (Day 7 ± 1, Day 14 ± 2, Day 21 ± 2, Day 28 ± 2 days) or at termination if early. ECG: At Day 14 and Day 28 (or at termination if early).
31-97-202 A phase III double-blind placebo-controlled study of aripiprazole in the treatment of psychosis, with risperidone as active control	Multicenter 4-week study, 404 hospitalized patients in acute relapse with diagnosis of schizophrenia or schizoaffective disoder, with a history of responding to neuroleptics. After a 5-day placebo washout patients were randomized to one of four oral treatment arms: 20 or 30 mg aripiprazole, 6 mg/day risperidone (titrated upward on 1st 3 days), or placebo. Doses were fixed and could not be modified during the study. Aripiprazole was administered once daily after breakfast with placebo after the evening meal, risperidone was administered twice daily, after breakfast and after meal in the evening.	2 samples per patient were scheduled, at day 14 and day 28 (or at termination if early). In addition, samples had to be drawn upon returning to the clinic after being out on pass.	PANSS: At screening, baseline, and at the end of each week (Day 7 ± 1, Day 14 ± 2, Day 21 ± 2, Day 28 ± 2 days) or at termination if early. ECG: At Day 14 and Day 28 (or at termination if early).

3.1 Design of Studies and Data Collection, continued

The below is reproduced from Volume 1.84 p. 61 of the NDA.

Study Number	Design/Duration of Dosing	Number and timing of PK samples	PANSS and ECG assessments
31-97-203 An open-label follow-on study of the long-term safety of aripiprazole in patients with psychosis	Multicenter long-term study in predominantly outpatient setting, 350 patients who participated in Study 31-97-201 or 31-97-202. Patients started as inpatients, and were discharged from the hospital to continue as outpatients upon achieving stabilization of psychosis. Patients started with 30 mg aripiprazole. Once a patient was suitably stabilized at the 30 mg dose, the investigator might adjust the dose within the range of 5-30 mg per day.	2 samples per patient were scheduled during in-hospital period: on Day 1 and Day 3 (or at discharge if earlier). One sample was scheduled at Week 1 follow-up visit. In addition, samples had to be drawn upon returning to the clinic after being out on pass.	PANSS scores and ECGs were not utilized in the analysis
31-94-202 A dose ranging study of the efficacy and tolerability of OPC-14597 in acutely relapsing hospitalized schizophrenic patients	Multicenter 4-week study, 250 hospitalized chronic schizophrenic patients in acute relapse, with a history of responding to neuroleptics. After a 3 to 7 day placebo washout, patients were randomized to one of three oral doses of aripiprazole: 2 mg, 10 mg, and 30 mg per day, one dose of haloperidol at 10 mg/day (5 mg on days 1 and 2), or placebo. Doses were fixed and could not be modified during the study (except the first day, when half of the assigned dose was administered). Aripiprazole was administered once daily after breakfast.	Peak blood sample was scheduled every week. Three additional samples were scheduled on Day 21.	PANSS: At screening, baseline, and at the end of each study week ± 2 days. ECG: ECGs were not utilized in the analysis
31-93-202 Efficacy and tolerability of ascending doses of OPC-14597 compared to placebo and to haloperidol in acutely relapsing hospitalized schizophrenic patients	Multicenter 4-week study, 69 hospitalized chronic schizophrenic patients in acute relapse, with no history of not responding to neuroleptics. After a 3 to 7 day placebo washout, patients were randomized to one of three oral treatment arms: aripiprazole, haloperidol, or placebo. Doses of aripiprazole and haloperidol were gradually increased during the first two weeks, from 5mg to 30 mg for aripiprazole, and from 5 mg to 20 mg for haloperidol. Then they were kept constant through the remainder of the study. Doses were administered once daily after breakfast.	One sample was scheduled every week. Two additional samples were scheduled on Day 21.	PANSS: At screening, baseline, and at the end of each study week ± 2 days. ECG: ECGs were not utilized in the analysis

3.2 Analytical Methods

Selected summaries of the performance of the analytical methods for each of the 5 studies that contributed samples to the population PK dataset are included as Appendix 1. to this review.

3.3 Data Collected and Data Editing

Appendix 2. of this review gives a detailed description of the Applicant's data collection and preparation for the analysis.

3.4 Model Selection

3.4.1 Pharmacokinetics

Appendix 3. gives a detailed description of the Applicant's pharmacokinetics model selection strategy.

The final model occurs on Volume 1.84 p. 46 of the NDA and the final parameter estimates appear on Volume 1.84 p. 79 of the NDA. These results yield the final model:

$$Cl\ (L/h) = 3.81 * [1 + 0.498*(LBW - 65)/65)]$$

$$V\ (L) = 293*e^{[0.309*(AGE - 39)/39 + 0.754(WTB - 81)/81]}$$

$$Ka\ (h^{-1}) = 1.06$$

3.4.2 Pharmacodynamics: QT-interval

Appendix 4. gives a detailed description of the Applicant's QT-interval model selection strategy.

There are 18 final models (2 datsets * 3 correction factors * 3 time windows = 18 models). These 18 models occur on Volume 1.84 pp.95 -97 of the NDA are reproduced in Appendix 4.

3.4.3 Pharmacodynamics: PANSS

Appendix 5. gives a detailed description of the PANSS model selection strategy.

The final model occurs on Volume 1.84 p. 46 of the NDA and the final parameter estimates appear on Volume 1.84 p. 79 of the NDA. These results yield two similar models, one for aripiprazole monotherapy and one for aripiprazole with co-administration of lorazepam:

Applicant's Final PK/PD models: PANSS Score = $PANSS_{baseline} + EFF_{PLAC} + EFF_{DRUG}$		
	monotherapy	concomittant lorazepam
EFF_{PLAC} [1]	$[-2.66 + (PANSS_{baseline} - 93)*(-0.0878)]*DUR^{0.371}$	$[-2.66 + (PANSS_{baseline} - 93)*(-0.0878) + 1.82]*DUR^{0.371}$
EFF_{DRUG} [1]	$-1.65*DUR^{0.494}$	$-1.65*DUR^{0.5718}$
[1] DUR = duration of teatment (Days)		

Table ST-36 on Volume 1.84 p. 46 of the NDA uses the model to derive the median decrease in PANSS for patients with a median baseline PANSS ($PANSS_{baseline} = 93$) treated for 30 days. The median is 18.2 points in the absence of lorazepam and 14.5 points with co-administration of lorazepam.

3.5 Applicant's Conclusions

The below is reproduced from Volume 1.84 p. 56 of the NDA.

8 **CONCLUSIONS**

- The pharmacokinetics of aripiprazole were described by a linear one-compartment model with first-order absorption.
- Although clearance was related to lean body weight, and volume of distribution was related to weight and age, these dependencies are unlikely to be clinically important.
- The estimates of the apparent oral clearance in patients were similar to those for normal volunteers.
- The results of the analysis indicated that no dose adjustments are needed based on demographic variables.
- Although the analysis indicated no dosage adjustment for any of the medications co-administered with aripiprazole, the number of patients on the concomitant medications, except benzodiazepines, was too small to be conclusive.
- The change from baseline of the total PANSS score in patients taking aripiprazole was described as the sum of change due to placebo and change due to the aripiprazole. Both effects (decrease from baseline) increased with duration of dosing during the study.
- The placebo effect increased with increasing baseline score, and was lower in patients who administered lorazepam concomitantly.
- The total effect of the drug (placebo and aripiprazole effect) was significantly higher in patients with higher baseline score, and lower in patients with concomitant lorazepam administration.
- The modeling indicated that neither exposure nor dose was found to correlate well with the efficacy of aripiprazole.
- No relationships could be determined between the change from baseline of QTCB, QTCF or QTCn and the corresponding plasma concentrations of aripiprazole.
- There was no prolongation of QTc in patients on aripiprazole, regardless of the algorithm used to calculate QTc.
- The variability in changes from baseline of QTc in aripiprazole patients was comparable to that in placebo patients.

4.0 Reviewer's Analysis

4.1 Analytical Methods

All of the % CVs for the standard and quality control samples that were accepted are below 20% and nearly all are below 15% (Appendix 1. shows some of these data). For the purposes of these exploratory analyses, the analytical methods are acceptable.

4.2 Data Editing and Checking

As a check for potential erroneous data, graphs and a table were produced from the data files and inspected. No potentially erroneous data were detected. The graphs were produced in Microsoft® Excel 97 SR-2 (h) and are reproduced in Appendix 6.

4.3 Models Selection

4.3.1 Pharmacokinetics

The Applicant's final model was reproduced by the Reviewer -- within rounding, the Reviewer's results were identical to the Applicant's. Using the Applicant's final model, the Reviewer then investigated the impact of each of the covariates identified in section **2.0 Reviewer's Objectives.** The full output from these NONMEM runs is included as 7. of this review. Table 1. below shows that two covariates improved the model signficantly significantly (> 3.84 point decreae in objective function, $p < 0.05$): smoking status and gender. The changes in clearance due to smoking and gender were both small (22% and 11%. respectively) and a standard error for either of the small estimated effects could not be obtained.

The demographic variable RACE was assigned 5 values: Caucasian, Black, Hispanic, Asian and Other. There were not significant differences between the known races, but the RACE=5 (other) category showed a 48% increase in clearance relative to RACE≠5. A decrease in objective function of 5.6 also occurred. However, visual examination of a plot of ETA_{CL} versus RACE showed no clear difference between RACE=5 and RACE≠5. Based on "other" not being a legitimate category, the small change in objective function, and the lack of trend in the ETA_{CL} versus RACE plot, it appears that there is little or no change in clearance as a function of race.

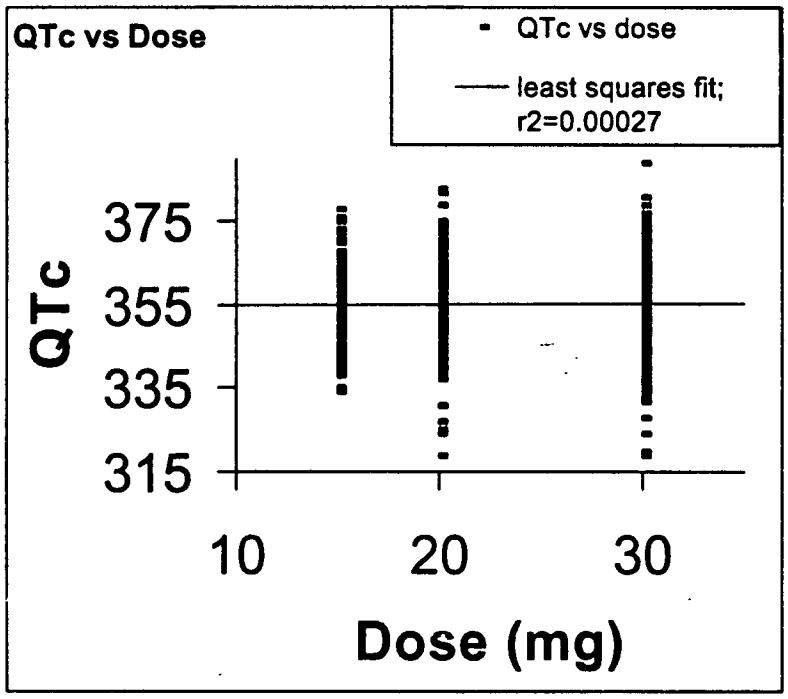
TABLE 1. FDA POPULATION PK MODELING RESULTS

description/output file		OBJF			
Applicant's Final Model	**est**	22063.891			
FDA – Applicant's Final Model/ 262.out	**est**	22063.892			
FDA -- age on CL/ 262ageoncl.out	**est**	22062.434			
			CL (L/h) for RACE ≠ 5	**CL (L/h) for RACE = 5**	**CL for RACE=5/ Cl for RACE≠5**
FDA – race on CL/ 262raceoncl3v4.out	**est**	22053.259	3.79	5.64	1.48
	SE est		not obtainable	not obtainable	
			CL (L/h) for non-smokers	**CL (L/h) for smokers**	**CL for smokers/ CL for non-smokers**
FDA -- smoke on CL/ 262smokoncl.out	**est**	22037.781	3.45	4.22	1.22
	SE est		not obtainable	not obtainable	
			CL (L/h) for males	**CL (L/h) for females**	**CL for females /CL for males**
FDA – sex on CL/ 262sexoncl.out	**est**	22059.301	3.84	3.4	0.89
	SE est		not obtainable	not obtainable	

4.3.2 Pharmacodynamics – QT-interval

A non-linear mixed effects model was used to correct the QT-interval data for changes in heart rate (RR-interval). The full output from these NONMEM runs is included as Appendix 8. of this review.

The change in corrected QT-interval (QTc) as a function of aripiprazole dose is plotted below. The results of the linear regression of QTc on dose (least squares fit in graph) are included in Appendix 8. The Reviewer concludes that, within the dose range studied, there is no easily discernable relationship between aripiprazole dose and QTc-interval.



4.3.3 Pharmacodynamics – PANSS

The Applicant's final model was reproduced by the Reviewer -- within rounding, the Reviewer's results were identical to the Applicant's.

The Reviewer used the Applicant's final model to calculate the placebo effect for a patient with a median $PANSS_{baseline}$ (PANSS = 93) treated for 30 days with or without lorazepam. The median decrease is 18.2 points in the absence of lorazepam and 14.5 points with co-administration of lorazepam. These reductions include the placebo effect: a 9.4 point reduction for monotherapy and a 3.0 point reduction with concomittant lorazepam treatment.

4.4 Reviewer's Conclusions

Consistent with the Applicant not having a pre-specified analysis plan, these analyses should be considered exploratory.

The Applicant's population pharmacokinetic model is reasonable. However, there appears to be a statistically significant, but fairly small (22%) increase in clearance for smokers relative to non-smokers which the Applicant does not include in their model. There also appears to be a statistically significant, but even smaller (11%) decrease in clearance for females relative to males which the Applicant does not include in their model. The magnitude of these changes (small) and an inability to estimate the precision of the changes (covariance matrices were not obtainable), caution against attempting to adjust dose due to these results.

The Applicant treated QT-interval data with the common correction factors (Bazett's = 0.5, Fredericia's = 0.33 and HFD-150's = 0.37). Regardless of the correction employed, no change in QT as a function of dose or concentration could be detected. Rather than use the common correction factors, the FDA Reviewer used a population modeling approach to arrive at individual corrected QT values. Similar to the Applicant, no change in corrected QT as a function of dose or concentration was detected.

The Applicant's population pharmacodynamic (PANSS) model is reasonable. Neither dose nor any other measure of exposure described the ability of aripiprazole to decrease PANSS score. Rather, PANSS score was a function of baseline PANSS, duration of treatment and concomitant lorazepam administration.

5.0 Comments and Recommendations

5.1 Comments and Recommendations to the Medical Officer

Consistent with the Applicant not having a pre-specified analysis plan, these analyses should be considered exploratory.

All of the comments below should be interpreted within the context of the doses and duration of treatment used in the 5 studies that contributed to the analysis. The dose range was from 2 to 30 mg per day (15 –30 mg QD for the QTc analysis) and the length of the studies was 4 weeks. The ability to extend the results to doses and treatment lengths outside the studied ranges is unknown.

Consistent with the Applicant's results, there was no clear relationship between age, gender, or race and pharmacokinetics. In contrast to the Applicant's results, the Reviewer's analysis shows a small increase in clearance (22%) may occur in smokers and females may have a slightly lower clearance (11% decrease) than males. These conclusions of differences due to smoking and gender are not firm and, if present, appear slight. The Reviewer does not recommend any change in labeling or any additional studies of these issues.

In agreement with the Applicant, QTc did not appear to be a function of aripiprazole dose.

The Reviewer found the Applicant's PANSS model reasonable. Administration of aripiprazole appeared to decrease PANSS scores. However, there was no evidence of a relationship between aripiprazole dose or concentration and decrease in PANSS. The drug-induced decrease in PANSS was increased (a greater decrease occurred) as duration of treatment increased. The decrease was hampered (a lesser decrease occurred) by concomitant lorazepam administration. The Applicant used the model to derive the median decrease in PANSS for a patient with a median baseline PANSS ($PANSS_{baseline}$ = 93) treated for 30 days. The median decrease is 18.2 points in the absence of lorazepam and 14.5 points with co-administration of lorazepam. These reductions include the effects of placebo and lorazepam: a 9.4 point reduction for placebo in the absence of lorazepam and a 3.0 point reduction for placebo in the presence of lorazepam.

Appendix 1. Applicant's Analytical Methods

The below is reproduced from Volume 1 of the submission of 17-Jan-02, p. 85.

OPC-14597
Study 31-93-282

Table 1-1. OPC-14597 in Plasma Assay Validation Performance of Standard Curve [5.00–600.00 (ng/mL)] Quality Control Standards

Between Batches (N=6)	5.00 * (ng/mL)	15.00 * (ng/mL)	150.00 * (ng/mL)	560.00 * (ng/mL)
Batch 1:				
Mean	4.52	13.50	169.39	526.04
S.D.	0.54	0.76	2.54	5.39
%C.V.	11.9	5.6	1.5	1.0
%Recovery	90.4	90.0	94.4	93.9
Batch 2:				
Mean	4.51	13.79	173.50	544.50
S.D.	0.42	0.62	7.00	19.21
%C.V.	10.3	4.5	4.0	3.5
%Recovery	90.2	91.9	96.4	97.2
Batch 3:				
Mean	4.85	13.90	169.46	515.52
S.D.	0.50	0.74	5.56	15.90
%C.V.	10.3	5.3	3.3	3.1
%Recovery	97.0	92.7	94.1	92.0
Batch 4:				
Mean	5.00	14.70	169.15	529.16
S.D.	0.40	1.60	8.96	31.17
%C.V.	8.0	10.9	5.3	5.9
%Recovery	100.0	98.0	94.0	94.5
Batch 5:				
Mean	4.73	13.95	168.82	538.09
S.D.	0.51	0.52	9.90	26.27
%C.V.	10.8	3.7	5.9	4.9
%Recovery	94.6	93.0	93.8	96.1
Batch 6:				
Mean	4.59	13.69	165.65	527.23
S.D.	0.42	0.32	5.13	8.79
%C.V.	9.2	2.3	3.1	1.7
%Recovery	91.8	91.3	92.0	94.1
Among Batches (N=36)				
Mean	4.70	13.92	169.41	530.06
S.D.	0.47	0.88	6.86	20.73
%C.V.	10.0	6.3	4.0	3.9
%Recovery	94.0	92.8	94.1	94.7

*: theoretical concentration.

(Ref: p 12–13 of the KCAS report No. V0718P1)

Appendix 1. Applicant's Analytical Methods, continued

The below is reproduced from Volume 1 of the submission of 17-Jan-02, pp. 86-87.

OPC-14597
Study 31-93-202

Table 1-2. Precision, Accuracy and Sensitivity of aripiprazole (OPC-14597) assay in Human Plasma *

Statistical Variable	Dilution Factor			Freeze/Thaw Cycle	
	2[nd] 800 ng/mL	5[th] 800 ng/mL	10[th] 800 ng/mL	20 ng/mL	360 ng/mL
Mean	801.84	759.28	782.41	17.28–19.41	313.11–348.98
S.D.	31.39	34.36	57.67	0.74–1.56	5.45–37.76
% C.V.	3.90	4.50	7.40	3.90–8.00	1.60–11.80
% Recovery	100.2	94.9	97.8	86.4–97.1	87.00–96.90

*: using OPC-14558 as internal standard.
[a] (500 µl + 500 µl) [b] (200 µl + 800 µl) [c] (100 µl + 900 µl)
(Ref: p 14–15 of KCAS report No. V0718P1)

OPC-14597
Study 31-93-202

of 9.21 for aripiprazole and the percent recovery ranging from 86.7 to 119.0 (etailed information in KCAS document No. I0786P1).

Table 2.2-1. Precision, accuracy and sensitivity of aripiprazole assay in Human Plasma *

Quality Assurance Standards (ng/mL)[a]	Statistical Variable				
	N	Mean	S.D.	% C.V.	% Recovery
12.27	12	10.65	0.35	3.3	86.8
14.40	30	17.13	2.39	14.0	119.0
16.00	9	16.43	2.97	18.1	102.7
240.00	40	234.84	12.23	13.6	100.65
245.40	11	212.86	6.83	3.2	86.7
506.10	11	465.18	12.58	2.7	91.90
560.00	40	570.17	44.38	10.3	110.05

*: using OPC-14558 as internal standard.
[a]: theoretical concentration.
(Ref: p 59–62 of the KCAS report No. I0786P1)

Appendix 1. Applicant's Analytical Methods, continued

The below is reproduced from Volume 2 of the submission of 17-Jan-02, pp. 106-107.

The mean recoveries ranged from 92.8 to 94.7 % while the % CV ranged from 3.9 to 10.0 %. The validation results indicate acceptable within-batch (Reference 1, Page 12) and among-batch precision and accuracy (Reference 1, Page 13).

Table 1-2. OPC-14597 in Plasma: Quality Control Sample Performance During the Method Validation

Within Batches (N=6)	5.00 ng/mL	15.00 ng/mL	180.00 ng/mL	560.00 ng/mL
Mean	4.51-5.00	13.50-14.70	165.65-173.50	515.32-544.50
Std. Dev.	0.40-0.54	0.32-1.60	2.54-9.90	5.39-31.17
% C.V.	8.0-11.9	2.3-10.9	1.5-5.9	1.0-5.9
Accuracy	90.2-100.0	90.0-98.0	92.0-96.4	92.0-97.2
Among Batches (N=36)				
Mean	4.70	13.92	169.41	530.06
Std. Dev.	0.47	0.88	6.86	20.73
% C.V.	10.0	6.3	4.0	3.9
Accuracy	94.0	92.8	94.1	94.7

Table 1-3. Precision, Accuracy and Sensitivity of OPC-14597 in Human Plasma *

Statistical Variable	Dilution Factor			Freeze/Thaw Cycle (Third Cycle Results)	
	2(a) 800 ng/mL	5(b) 800 ng/mL	10(c) 800 ng/mL	20 ng/mL	360 ng/mL
Mean	801.84	759.28	782.41	17.28-19.41	313.11-348.98
Std. Dev.	31.39	34.36	57.67	0.74-1.56	5.45-37.76
% C.V.	3.9	4.5	7.4	3.9-8.0	1.6-11.8
Accuracy	100.2	94.9	97.8	86.4-97.1	87.0-96.9

*: OPC-14558 as internal standard.
a: (500 µL + 500 µL) b: (200 µL + 800 µL) c: (100 µL + 900 µL)

Appendix 1. Applicant's Analytical Methods, continued

The below is reproduced from Volume 2 of the submission of 17-Jan-02, p 110.

Three sets of quality control (QC) samples were prepared in a manner blinded to the analytical staff, and analyzed along with the clinical samples to ensure compliance of the ~ method. The summary of the results is presented in Table 3-2 (reference 3, pages 168-171). Based on the QC sample results, the assay was found to have adequate precision (percent coefficients of variation between 5.8 and 9.4 %) and accuracy for OPC-14597 (% recovery ranging between 103.5 % and 104.0 %).

Table 3-2 Precision, Accuracy and Sensitivity Data for OPC-14597 in Human Plasma During Sample Analysis

Lab QC Code #	2	1	3
OPC-14597 concentration	13.50 ng/mL	180.00 ng/mL	540.00 ng/mL
Mean	14.04	186.36	561.22
Std. Dev.	1.32	11.97	32.60
% CV	9.4	6.4	5.8
% Accuracy	104.0	103.5	103.9
N	121	119	119

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Appendix 2. Applicant's Data Collected and Data Editing

The below is reproduced from Volume 1.84 p. 23 of the NDA.

3.1.4 Data Preparation

In total, 4226 plasma samples for 1135 patients on aripiprazole were obtained from 5 studies:

Study 31-97-201:	204 patients and 631 concentrations;
Study 31-97-202:	202 patients and 664 concentrations;
Study 31-97-203:	515 patients and 1501 concentrations;
Study 31-94-202:	180 patients and 1255 concentrations.
Study 31-93-202:	34 patients and 175 concentrations.

The original SAS [9] data sets with plasma concentrations, sampling times, dosing (amounts, dates and times), demographic, vital signs, clinical laboratory and concomitant medications information for each study were merged together by study, patient identifier, date and time. The structure and content of the data sets were different for each study. Therefore, merging was study-specific and was done separately for each study (see Appendix II).

The following assumptions were used in the creation of the data set for the analysis:

1. For open label Study 31-97-203 only plasma samples drawn during the first 7 days (in-patient portion) of the study were used in the pharmacokinetic analysis.

2. Plasma samples drawn earlier than the first dose or later than 3 days after the last dose were excluded from the analysis. The studies were not designed to obtain samples later than the last dose, and samples that appeared to be drawn later (most of them much later) were assumed to be erroneous.

3. Patients were considered non-compliant if they had BQL concentrations, other than for blood sample taken prior to the first dose. All samples of non-compliant patients taken later than the first BQL value were excluded from the analysis (except for post dose BQL value on the first day: the value was excluded, but the later concentrations were kept in the data).

4. Only times of the first 5 doses (Days 1-5) were available in Studies 31-97-201, 31-97-202, and 31-97-203. In Studies 31-97-201 and 31-97-202, the first post-dose sample was drawn at Day 14. Therefore, median dosing time for a patient (over first 5 doses) was used as dosing time in the studies. If all dosing times were missing for a patient, then the median in the population of the study (over all median times) was used.

5. In Studies 31-94-202 and 31-93-202 time of each dose that immediately preceded a sample was recorded. An unknown dosing time was imputed by propagation backwards from the next known dosing time. For doses administered later than the last known dosing time, propagation forward from the last known dosing time was employed.

6. In Study 31-93-202, the date of the dose that preceded the sample was not recorded. This date was assumed to coincide with the date of the corresponding blood draw,

The below is reproduced from Volume 1.84 p. 24 of the NDA.

except for the first sample on Day 21, where it was assumed that the dose date was one day earlier than the sample date.

7. Doses were assumed to be administered once-a-day. In the studies 31-97-201 and 31-97-202 the information was recorded about the number of missed tablets on each day a tablet was missed. In these studies patients were administered two aripiprazole tablets of equal strength, except for patients on 15 mg aripiprazole of Study 31-97-201. For them, one of the administered tablets was aripiprazole, the other tablet was placebo. Therefore, for all aripiprazole patients in these studies except for the group mentioned above, it was assumed that if two tablets were missed, the dose on that day was missed; if only one tablet was missed the dose was set to half the assigned dose. In the 15 mg aripiprazole group of Study 31-97-201, it was unknown whether one missed tablet was a placebo or aripiprazole, so the dose was not assumed to have been missed.

8. A patient was assumed to be a Drinker (and assigned ALCO=1) if he/she was coded as either Drinker or Ex-drinker in the original demographic data. In addition, if any laboratory test for blood alcohol was positive for a patient, that patient was coded as a drinker (ALCO=1) regardless of his/her alcohol record in the demographic data set.

9. Missing values for alcohol consumption, smoking and creatine kinase were not imputed (All three were not recorded in 31-93-202, alcohol consumption and smoking were not recorded in 31-94-202). They were assigned a separate value of "-1".

10. A separate value of "-1" was assigned to baseline total PANSS scores of patients in Study 31-97-203, since that data was not available.

11. Patients were assumed to be non-smokers if they never smoked or quit smoking not less than six months before the study.

12. For patients with missing values of height, median height over aripiprazole and placebo patients of same gender in the respective study was used.

13. Weight at baseline was used as weight covariate. If it was missing for a patient, then weight at screening was used. If also missing, median of baseline weights over all subjects of the same gender in the study was used.

14. Baseline laboratory values were used as covariates. For a few missing baseline values, a baseline value was imputed by the median of all measurements for a subject. If missing, the value was imputed by the population median of baseline values over all patients of same gender in the study.

15. In addition to Cockroft-Gault [10] equation, creatinine clearance was estimated according to Salazar-Corcoran equation [11] as follows:

Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 25 of the NDA.

For males:
CSAL = (137-AGE)*(0.285*WT + 12.1*(HT*HT/10000))/51/CREA
For females:
CSAL = (146-AGE)*(0.287*WT + 9.74*(HT*HT/10000))/60/CREA

Here AGE is age (years), WT is weight (kg), HT is height (cm), and CREA is plasma creatinine (mg/dL).

This is a more accurate equation than the Cockroft-Gault equation for estimating creatinine clearance in obese patients, and it is equally precise for normal healthy subjects [12].

16. Plasma samples were assumed to be affected by concomitant medications if they were drawn after start, but not later than 7 days after stop of the respective medication. For illegal drugs and benzodiazepines detected in blood, plasma samples were assumed to be affected from the date of a positive blood test until 7 days after the test.

17. If a patient had a positive result on illegal drug screen (plasma or urine), benzodiazepines or alcohol tests (clinical laboratory data) anytime after screening in studies 31-97-201 and 31-97-202, or in the window of less than 7 days before start and 7 days after start in study 31-97-203, he/she was assigned to the respective covariate group (concomitant medications or drinker status, respectively).

In addition, a number of data manipulations were performed to clean the data and to conform to the NMTRAN/ NONMEM [13] format. All the data manipulations for the creation of the data set are detailed in table ST-2. Table ST-3 accounts for the records excluded from the file for the analysis. Additional details about excluded records can be found in table ST-4 and in Appendix II.

The created pharmacokinetic data file (pk.csv) for NONMEM analysis contained 2563 plasma samples from 694 patients as follows:

Study 31-97-201: 391 concentrations from 171 patients;
Study 31-97-202: 415 concentrations from 175 patients;
Study 31-97-203: 469 concentrations from 148 patients;
Study 31-94-202: 1137 concentrations from 170 patients;
Study 31-93-202: 151 concentrations from 30 patients.

During the preliminary exploration of the data file 3 erroneous observations were detected (see details in table ST-5). They were excluded, and the new file pk_mod1.csv was used for modeling.

Two more data sets with minor changes were also used (see details in table ST-5):
1. During refinement of the covariate model a data set pk_mod1_subwt.csv was temporarily used. This data set was created from pk_mod1.csv by excluding (commenting out) observations of three patients with the highest weights.

Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 26 of the NDA.

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2. There was an error in merging concentrations and concentration times on Day 21 of Study 31-93-202. The error affected times of two concentration points of one aripiprazole patient. The corrected data set, pk_mod1_cor1.csv was used to re-run the final model.

3.1.5 Patient demographics and data summaries

The summaries of demographic characteristics for patients present in the data set for pharmacokinetic analysis are presented in tables ST-7 and ST-8. Figures SF-1, SF-2, and SF-3 show the scatter plots of available concentrations: concentration versus duration of dosing (SF-1 and SF-2) and versus time after last dose before the sample (SF-3) by study and dose group.

Table ST-9 presents a summary of concomitant medications in the pharmacokinetic data set. It shows number of patients that had at least one concentration affected by the concomitant medication. There were less than 15 patients on ketoconazole (14), haloperidol (12), and clonazepam (14), and there were no patients with concomitant magnesium hydroxide.

3.2 Data for PK/PD analysis

The data from four double-blind studies used for pharmacokinetic analysis were also used in the PK/PD analysis. In addition to patients on aripiprazole, the data from the placebo patients were also used in the analysis. Beside dosing, sampling, and covariate information used in the pharmacokinetic analysis, the data for PK/PD analysis also included the efficacy variable (total PANSS score). Table ST-1 lists the schedule of the efficacy evaluations for each of the studies.

All the covariates evaluated in pharmacokinetic analysis were also included in PK/PD analysis.

3.2.1 Data preparation

In total, original data sets from Studies 31-97-201, 31-97-202, 31-94-202, and 31-93-202 contained 3812 measurements of total PANSS score from placebo and aripiprazole patients (table ST-3). These records were added to the sampling and dosing information for each patient.

The following assumptions were used in the creation of the data set for the analysis:

1. If time of the PANSS measurement was missing in Studies 31-97-201 and 31-97-202, it was imputed with a median time of measurements for a patient. If all times were missing for a patient, then the median in the population of the study (over all median times) was used.
2. In Studies 31-94-202 and 31-93-202, the time of the PANSS score measurement was not recorded. It was assumed to be 09:00 for all the measurements in these studies.
3. Concomitant medications available in the pharmacokinetic analysis were also studied for their possible direct influence on pharmacodynamic response (not through influence on aripiprazole exposure). As in the pharmacokinetic analysis, PANSS

Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 27 of the NDA.

scores were assumed to be affected by concomitant medications if they were assessed after start, but not later than 7 days after stop of the respective medication. For illegal drugs and benzodiazepines detected in blood, PANSS scores were assumed to be affected from the date of a positive blood test till 7 days after the test.

The following records were excluded from the combined data set for the analysis:

1. Measurements recorded 3 or more days before the drug (aripiprazole or placebo) start date;
2. Measurements recorded 3 or more days after the drug (aripiprazole or placebo) stop date. The studies were not designed to evaluate efficacy later than 24 hours after the last dose, and measurements that appeared to be drawn later (most of them much later) were due to the errors in dates or patient identification;
3. Measurements from patients with missing drug start date;
4. Measurements from aripiprazole patients with no pharmacokinetic sampling or dosing information;
5. Measurements of non-compliant patients recorded on or after their non-compliance started.

The exclusion of the observations for each of the studies is described in table ST-3. Additional details about excluded records can be found in Appendix II.

The final PK/PD file contributed 2472 scores from 582 aripiprazole patients and 1205 scores from 306 placebo patients (see table ST-6 for their distribution between the studies).

Several data sets were used in the PK/PD analysis:

1. The data set with only placebo patients (pd_plac.csv) was used to develop the placebo model;
2. The data set with dosing, pharmacokinetic and pharmacodynamic information only for patients on aripiprazole (pkpd1_act_mod2.csv) was initially used for PK/PD model development;
3. The PK data set pkpd1_act_mod2 _for_pktables.csv. This data set was identical to the data set pkpd1_act_mod2.csv except for NONMEM data items EVID and MDV that were set to be EVID=2 and MDV=1 for PANSS score observations. This data set was used to generate predictions of individual exposures at the time of PANSS measurements.
4. The data file with pharmacodynamic and individual exposure information for both placebo and aripiprazole patients (pd_both.csv) was used for developing the empirical model for exposure-effect relationships. To create this data set, first, the predictions of individual exposures at the times of PANSS score measurements were obtained from the final pharmacokinetic model using the data set pkpd1_act_mod2 _for_pktables.csv. The individual exposures were added to the PANSS score measurements from the pkpd1_act_mod2.csv data set, and then combined with the placebo data pd_plac.csv, where all exposure measures were set to zero.

The below is reproduced from Volume 1.84 p. 28 of the NDA.

3.2.2 Patient demographics and data summaries

The distribution of the baseline scores for the placebo patients is plotted in figure SF-4. Figure SF-5 shows the individual plots of total PANSS score versus duration of dosing for the placebo patients. The plots of total PANSS scores versus duration of dosing for patients in different aripiprazole groups (including placebo patients, where DOSE=0) are shown in figure SF-6. Figure SF-7 presents the individual plots of total PANSS scores versus duration of dosing for patients in the 30 mg dose group.

3.3 DATA FOR PHARMACOKINETIC/SAFETY ANALYSIS

The data from two double-blind studies, Study 31-97-201 and 31-97-202, which were used for pharmacokinetic analysis were also used in the pharmacokinetic/safety analysis. In addition to patients on aripiprazole, the data from the placebo patients were also used in the analysis. Beside the plasma concentration data, the data for the analysis included QTc intervals. In both studies twelve-lead ECGs were recorded at screening, and at Week 2 and Week 4 of the study. Cardiac QT intervals were corrected for heart rate using three approaches: correction by Bazett's method (QTCB), correction by Fredericia's method (QTCF), and the method recommended by the FDA Div of Neuropharm (baseline correction, QTCn). QTCn measurements were computed as

$$QTCn = QT/RR^{0.37},$$

where QT and RR denoted cardiac QT (msec) and RR (sec) intervals, respectively.

QTCB and QTCF measures were provided to [redacted] by the sponsor; QTCn measures were computed from QTCB and QTCF as described in Section 3.3.1.

3.3.1 Data preparation

Baseline corrected QTc (QTCn) values were computed from QTCB and QTCF as follows (see derivation in Appendix IV):

$$QTCn = QTCF^{(3-6*0.37)} * QTCB^{(6*0.37-2)}.$$

In total, there were 651 QTc observations recorded for aripiprazole patients and 516 measurements for 192 placebo patients in the clinical database. Measurements were recorded on Day 14, Day 28 and at Early Termination.

The concentrations from the data file for NONMEM pharmacokinetic analysis (pk_mod1_cor1.csv) were merged with the QTc data by patient number, date and time. Three different files were created based on the allowed time difference between the blood samples and the QTc measurements. Only QTc measurements performed within 2 hours of blood sampling (two-hour window) were retained in the first data file (SAS data set ful_qtn.sd2). The second (fulqtn12.sd2) and third (fulqtn48.sd2) data sets contained the QTc and concentrations that were apart from each other by no more than 12 and 48 hours, respectively (12-hour and 48-hour window). Thus, the first data file was a subset of the second and third, and the second data file was a subset of the third data file. In

Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 29 of the NDA.

addition, the data files contained the QTc measurements of placebo patients; for them concentrations were set to zero.

After merging the data, there were 251 QTc observations from 184 aripiprazole patients in the 2-hour window file, 506 observations from 313 aripiprazole patients in the 12-hour window file, and 616 observations from 328 aripiprazole patients in the 48-hour window data file.

The below is reproduced from Volume 1.84 p. 62 of the NDA.

ST-2 Additional data manipulations for the preparation of the pharmacokinetic NMTRAN/NONMEM file pk.csv not described in the text.

Merging	The SAS datasets with PK concentrations, PK sampling, dosing (amounts, dates and times), demographic, vital signs, clinical laboratory, efficacy and concomitant medications information were merged together by study, patient identifier, date and time. Since all the data sets had different structures, merging was study-specific and was done separately for each study.
Exclusions	• Missing time of blood draw. • Missing concentration values. • Samples from non-compliant patients (defined in Section 3.1.4). • Baseline (pre-first dose) plasma samples. • Plasma samples and PANSS scores for a patient recorded later than 3 days after the last study dose. • All records for a patient later than 7 days from start of dosing in 31-97-203. • Dosing records that were chronologically later than the last PK or PD measurement for a patient. • Only baseline (earliest) measurements were retained for all laboratory values. • Plasma samples recorded to be drawn at the same time, but with different concentration values (listed as inconsistent concentrations in table ST-3).
Value changes	• Blood draw times and dose times recorded as blank, NK:NK, or ND:ND were coded as missing. • Dosetime recorded as "9 :00" was re-coded as "09:00". • Amount coded as '2 TABS' or '30 MG' in 31-97-201 was re-coded as 30. • Hard-coded manipulations (changes, imputations or deletions) for several cases (see ST-4 for description of each case).
New covariates: assignments and computations	• Body Mass Index (BMI) was computed as BMI (Kg/m^2)= 10000*WT (kg) /HT^2 (cm^2) • Body Surface Area (BSA) was computed according to [26] BSA(m^2) =exp(-3.751+0.422*log(HT (cm))+0.515*log(WT (kg))) • Creatinine clearance (CRCL and CSAL) was computed according to [10] and [11] For Males IBW (kg) = 50 + 0.92* max(0, HT (cm) -152) CRCL (mL/min) = (140-AGE)*IBW (kg) /72/CREA (mg/dL) CSAL (mL/min) = (137-AGE)*(0.285*WT (kg) + 12.1*(HT^2 (cm^2)/10000))/51/CREA (mg/dL) For Females IBW = 45 + 0.92* max(0, HT-152) CRCL= 0.85*(140-AGE)* IBW /72/CREA (mg/dL) CSAL = (146-AGE)*(0.287*WT + 9.74*(HT*HT/10000))/60/CREA (mg/dL)

Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 63 of the NDA.

	• Dose group (GRP) was assigned as following: a. according to randomization for Studies 31-97-201, Studies 31-97-202, and Studies 31-94-202; b. as 30 mg in 31-93-202; c. missing (.) in 31-97-203. Duration of dosing (DUR) was computed as difference in days between the event and the first study dose for each patient (including placebo patients in PK/PD analysis)
Imputation of missing values	• In Studies 31-97-201, 31-97-202 and 31-97-203 median time of the first 5 doses for a patient was used for all doses. If missing, median population dose time (over all median times) in the respective study was used. • In Studies 31-94-202 and 31-93-202, the unknown dosing time was imputed by propagation backwards from the next known dosing time. For doses administered later than the last known dosing time, propagation forward from the last known dosing time was employed. • Missing height was imputed with the median value among all patients of the same gender in the study. • Weight at baseline was used as weight covariate. If it was missing for a patient, then weight at screening was used. If also missing, median of baseline weights over all subjects of the same gender in the study was used. • A missing laboratory baseline value was imputed by the median of all the measurements for a subject. If missing, the value was imputed by the population median of baseline values over all patients of same gender in the study. • Missing smoking status, alcohol consumption, baseline creatine kinase, and baseline total PANSS score were coded as –1.

The below is reproduced from Volume 1.84 p. 64 of the NDA.

ST-3 Accounting of records during creation of the data sets for analysis

	Study				
	31-97-201	31-97-202	31-97-203	31-94-202	31-93-202
DEMOGRAPHICS					
Patients in the original data set	204/106[a]	202/103[a]	515[b]	180/64[a]	34/35[a]
Excluded patients with missing drug start or stop date	1/2	1/0	172	0	0
Excluded patients on aripiprazole dosing but no plasma data	15	9	NA[c]	8	3
PK					
All samples in original data set	1262[d]	1778[d]	3002	NA[d]	NA[c]
Excluded samples from not identified patients (discrepancy between dosing or demographic and plasma data)	0	50[f]	599	0	0
Original aripiprazole samples	631	664	1501	1255	175[g]
Excluded samples with missing drawtime	9	37	24	36	14[g]
Excluded samples with inconsistent aripiprazole concentrations[h]	6	2	10	0	0
Excluded samples with no or conflicting drug start date or no dose information	0	1	5	0	2
Excluded late samples	22[j]	10[j]	253[k]	0	0
Excluded baseline (pre- first dose) samples	184[l]	169[m]	121[n]	1	0
Excluded samples from non-compliant patients	10	19	16	2	0
Missing concentration values	9	11	4	79	9
Missed or partly missed doses[i]	25	44	NA	NA	NA
Total concentrations in the PK NONMEM file	391	415	469	1137	151[p]
Total aripiprazole patients in PK NONMEM file	171	175	148	170	30
PD					
Original PANSS scores (including placebo patients, excluding screening, not missing date, not missing PANSS score)	1295	1236	NA[o]	1007	274
Excluded early scores (>= 3 days before drug start)	1	1	NA[c]	4	1
Excluded scores with no drug start date, pk or dosing information	0	1	NA[c]	11	6
Excluded late scores in aripiprazole patients (>= 3 days after drug stop)	1	2	NA[c]	0	0
Scores of placebo patients	427	398	NA[b]	248	132
Excluded late scores of placebo patients (>= 3 days after drug stop)	1	1	NA[c]	0	0

Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 65 of the NDA.

	Study				
	31-97-201	31-97-202	31-97-203	31-94-202	31-93-202
Excluded observations from non-compliant patients	1	5	NA[c]	0	0
Total scores of aripiprazole patients in PKPD file[d]	803	790	NA[c]	744	135
Total scores of placebo patients in PKPD file	427	398	NA[c]	248	132
Aripiprazole patients with scores in PKPD file[e]	188				
Placebo patients with scores in PKPD file	104	103	NA[c]	64	35

a. Aripiprazole/placebo patients in demog.sd2 data set.
b. Aripiprazole patients in dose0.sd2 data set.
c. Not assessed.
d. Samples from aripiprazole patients only.
e. Samples from patients on aripiprazole, placebo and comparator drugs.
f. Samples from 16 patients not present in demographic data set.
g. Not including samples drawn at randomization.
h. No matched times associated with samples.
i. Two different concentrations results reported for a sample.
j. Three days or later after drug stop.
k. Of them, 252 later than 7 days after drug start and 1 later than 3 days after last drug administration.
l. Among them, 18 samples with concentration > 0, but time earlier than drug start.
m. Among them, 1 sample with concentration > 0, but drawn earlier than drug start.
n. Among them, 65 samples with concentration > 0, but drawn earlier than drug start.
o. Dose missed entirely or half of the dose administered, no samples excluded (see Section 3.1.4).
p. One concentration for patient 0090060 counted twice.
q. Including patients with PANSS score measurements, but no PK measurements.

Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 66 of the NDA.

ST-4 Handling of special cases.

Study	Patient	Description	Action
31-97-201	0310010	All measurements of weight are missing except Day 14 and Day 28	Impute weight with the median of two available measurements
31-97-203	0360008	Missing dose amount on 14DEC97	Delete concentrations after that date
	0360012	One dose was recorded in the data set smed0, but amount was missing. Drug start and stop were on the same date, no concentrations were found.	Delete
	0410011	Height missing	Imputed with height from 31-97-201 for this patient
	0600005	Height missing	Imputed with height from 31-97-202 for this patient
	0250004	Inconsistent date of start	Delete all data (1 concentration value)
	0570001	Inconsistent date of start	Delete all data (2 concentration values)
31-94-202	0010278	Baseline BQL value	Exclude
31-93-202	0020035	Dosedate is missing in smed0, but amount and visit number is present	Impute missing dosedate with the date of the respective visit (visitnr=22)

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Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 67 of the NDA.

ST-5 Nonmem data file modifications

	STUD[a]	ID (ptcode)	Description	Action
From pk.csv to pk_mod1.csv	10	109 (70140)	Last 2 concentrations drawn 70 and 77 hours after the dose were 5 times higher than all other concentrations. The preceding concentration, the highest except for these 2 measurements, was drawn 4 hours after the dose on 15th day of dosing (i.e., at or close to steady state). Two more doses were administered after that concentration, and 3 days later the last 2 high values recorded.	Exclude 2 concentrations on 5/30/95: at 7:20 and 14:10
	8	269 (230010)	There was a discrepancy in the original dosing file: start of dosing was recorded as 10/21/97, but the first dose was administered on 10/28/97. So, for the concentration record on 10/28/97, it is unclear when the last dose was administered.	Exclude concentration point on 10/28/97
From pk_mod1.csv to pk_mod1_subwt.csv	6	378 (340004)	Patients with the highest 3 weights (170, 193, and 202 kg, respectively	Exclude all their concentrations (2, 4, and 3 points, respectively)
	7,8	569 (710010)		
	6,8	382 (360008)		
From pk_mod1.csv to pk_mod1_cor1.csv	11	165 (110103)	In the data set pk.csv 2 concentration times on 4/10/95 were assigned erroneously (incorrectly merged).	Change TIME=11:15 and the first row for TIME=16:00 to 10:30 and 11:15, respectively.

a. Study numbers were coded as: 6 – 31-97-201, 7 – 31-97-202, 8 – 31-97-203, 10 – 31-94-202, 11 – 31-93-202.

ST-6 Distribution of patients with PANSS score measurements among the studies.

	Study			
	31-97-201	31-97-202	31-94-202	31-93-202
Number of PANSS score measurements of aripiprazole patients	803	790	744	135
Number of aripiprazole patients	188	191	172	31
Number of PANSS score measurements of placebo patients	427	398	248	132
Number of placebo patients	104	103	64	35

Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 68 of the NDA.

ST-7 Summary of patient demographics for continuous covariates (PK analysis)

Covariate[a]	Mean	SD	Median	Percentiles		Min	Max	NONMEM data item
				10%	90%			
Age (years)	38.7	9.80	39.0	25.3	52.0	18.0	68.0	AGE
Weight (kg)[b]	83.4	19.0	81.0	62.0	110	43.0	153	WTB
Lean body weight[b] (kg)	58.1	9.85	57.7	45.2	70.9	20.6	84.7	LBW
Body Mass Index[b] (kg/m^2)	28.2	6.78	26.9	20.9	37.2	15.3	61.2	BMI
Body Surface Area[b] (m^2)	2.00	0.249	1.99	1.70	2.33	1.37	2.83	BSA
Estimated creatinine clearance[c] (mL/min)	89.4	22.3	87.3	62.4	116	39.1	216	CRCL
Estimated creatinine clearance[d] (mL/min)	108	26.3	106	76.9	139	55.8	244	CSAL
Creatine kinase[e]	149	208	101	49.0	276	18.0	3960	CPK
Total protein (g/L)	7.39	0.556	7.30	6.70	8.10	5.70	9.70	PROT
Total bilirubin (mg/L)	0.607	0.216	0.600	0.40	0.900	0.00	2.00	BILI
Alkaline Phosphatase (mU/mL)	77.1	21.6	73.0	53.3	107	35.0	186	ALK
Aspartate aminotransferase (U/L)	20.7	12.4	17.0	12.0	31.0	5.00	124	SGOT
Alanine aminotransferase (U/L)	27.5	22.9	21.0	10.0	50.0	2.00	217	SGPT
Baseline total PANSS score[f]	94.2	17.8	93.0	73.0	118	49.0	169	bpd

a. Unless noted otherwise, summary is based on 694 patients with non-missing values from the data set pk_mod1.csv
b. Without 3 patients with the highest weight of 170, 193, and 203 kg
c. Estimated according to Cockroft – Gault equation [10]
d. Estimated according to Salazar – Corcoran equation [11]
e. Based on 664 patients with non-missing values
f. Based on 550 patients with non-missing values

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Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 69 of the NDA.

ST-8 Summary of patient demographics for categorical covariates (PK analysis)

Covariate	Count	Percent (%)	NONMEM data item
Gender (M/F)	503/191	72/28	SEX
Race (Caucasian/Black/Hispanic/Asian/Other)	396/217/53/15/13	57/31/8/2/2	RACE
Smoking (No/Yes/Missing)	123/371/200	18/53/29	SMOK
Alcohol consumption (No/Yes/Missing)	150/343/201	22/49/29	ALCO

Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 70 of the NDA.

ST-9 Number of patients with at least one plasma sample affected by a concomitant medication

Concomitant medication or group of medications	Patients	NONMEM data item
substrates and inhibitors of 3A4 isoform of P450 enzyme: amiodarone, cimetidine, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, fluvoxamine, gestodene, indinavir, nefazodone, and ritonavir	26	GRA
substrates and inhibitors of 2D6 isoform of P450 enzyme: fluoxetine, haloperidol, methadone, paroxetine, quinidine, ranitidine hydrochloride, chlorpheniramine, cimetidine, clomipramine, and levomepromazine	37	GRB
anti-acids: combination antacids and adsorbents, magnesium hydroxide, aluminum hydroxide, sodium bicarbonate, and calcium carbonate	133	GRC
proton pump inhibitors and H2 antagonists: famotidine, omeprazole, and lansoprazole	40	GRD
Substances of abuse: cannabinoids, cocaine, methadone, methaqualone, opiates, propoxyphene, sympathomimetic amines, phencyclidine, marijuana, barbiturates, digoxin, theophylline	20	GRE
Benzodiazepines: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam	72	GRG
ketoconazole	14	CA1
haloperidol	12	CB1
ranitidine hydrochloride	19	CB2
combination antacids and adsorbents	125	CC1
magnesium hydroxide	0	CC2
aluminum hydroxide	3	CC3
famotidine	21	CD1
omeprazole	15	CD2
lorazepam	539	CF1
clonazepam	14	CG1
temazepam	50	CG2