Clinical Pharmacology/Biopharmaceutics Review

NDA	21436/S018
Drug	Aripiprazole
PRODUCT (Brand Name):	Abilify
Sponsor	Otsuka
Reviewer	Andre Jackson
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SUBMISSION DATE:	March 23, 2007 August 28, 2007
NDA TYPE:	Pediatric Written Request

REVIEW OF POPULATION PHARMACOKINETIC STUDY

EXECUTIVE SUMMARY

Otsuka Pharmaceuticals is seeking approval for Aripiprazole for treatment of Schizophrenia in adolescents 13-17 yrs old and for Bi-Polar Disorder in children and adolescents aged 10-17 years. The overall findings of the reviewer are summarized below:

1. Pediatric pharmacokinetics for Aripiprazole are similar to those seen in adults

2. Is there a Dose/Exposure-response relationship for effectiveness with Schizophrenia?

No, the 10 mg and 30 mg doses appear to give the same response. The sponsor is proposing a [redacted]

3. Is there a Dose/Exposure-response relationship for effectiveness for Bi-Polar disorder?

There appears to be no dose response relationship for the YMRS scale.

4. Is there a Dose/Exposure-response relationship for safety-Schizophrenia?

For the two major side effects, somnolence and extrapyrimidal effects there was a dose effect..

5. Is there a Dose/Exposure-response relationship for safety-Bi-Polar?

For the two major side effects, somnolence and extrapyrimidal effects there was a dose response relationship observed based upon graphical analysis.

6. Is there a need to dose adjust for the lower weight children.

The observed distribution of plasma levels are similar for children above and below the median weight of 61 kg.

COMMENTS TO MEDICAL REVIEWER

There is no clear dose response for either indication so that the lower 10 mg dose appears to be as efficacious as the larger dose.

INTRODUCTION

Abilify™ (aripiprazole, OPC-14597, BMS-337039) is approved in the United States of America (US) for the treatment in adults of acute schizophrenia (November 2002), maintenance of stability in schizophrenia (August 2003), treatment of acute manic and mixed episodes associated bipolar disorder (September 2004), and for the maintenance of efficacy in bipolar I disorder (March 2005). Aripiprazole is also approved for the treatment of schizophrenia in the European Union, Australia, and a number of countries in Asia, Europe, and Latin America. It is being evaluated for the treatment of various psychiatric disorders in a collaborative program between Marketing Authorization Holder Otsuka Pharmaceutical Company (OPC) (Japan) and co-marketer Bristol-Myers Squibb Company (BMS).

The mechanism of action of aripiprazole differs from that of currently marketed typical and atypical antipsychotics. It has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial

agonism/antagonism at dopamine D2 and serotonin 5-HT1A receptors, and antagonism at serotonin 5-HT2 receptors. Aripiprazole has the properties of an agonist in an animal model of dopaminergic hypoactivity and the properties of an antagonist in animal models of dopaminergic hyperactivity. The emerging literature for other antipsychotics indicates that 5-HT1A activity may be correlated with the clinical observation of efficacy against negative symptoms in patients with schizophrenia. It seems likely that the favorable safety and tolerability profile of aripiprazole, including its low incidence of extrapyramidal symptoms (EPS), lack of prolactin elevation, decreased adrenergic and anticholinergic side effects, and decreased weight gain is also mediated by its unique profile of interaction with central neuroreceptors.

The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

OBJECTIVE OF THE ANALYSIS

The objectives of this population pharmacokinetic (PK) analysis were to:

1. describe the pharmacokinetics of aripiprazole in children and adolescent patients (ages 10-17)

2. investigate the impact of key covariates, especially size and age, on the pharmacokinetics of aripiprazole

3. estimate the between-subject and random residual variability

The estimated pharmacokinetic parameters were compared to historical adult population pharmacokinetic estimates.

METHODS

Overview of Study Designs

The current analysis consisted of modeling the PK of aripiprazole in children, adolescents and adults with bipolar I disorder or schizophrenia following oral administration of aripiprazole.

Protocol 31-03-238 was an Open-label Dose Escalation Study to Assess the Safety, Tolerability, and Pharmacokinetics of Orally Administered Aripiprazole Tablets in Children and Adolescent Patients. This study provided dense sampling for PK analysis. Seventeen patients completed the study; 20, 25, and 30 mg doses were administered. Serial samples after two weeks of dosing (i.e. at steady state) were collected between 0 and 24 hours post-dose. The two safety and efficacy studies, 239 and 240, were carried out at fixed doses of 10 and 30 mg following a titration phase. Study overview and sampling times are presented in Tables 1 and 2.

The Adult Dataset

The adult population PK dataset consists of a data file which contains 2563 plasma samples from 694 patients enrolled in the following 5 studies:

1.Protocol No. 31-93-202: Efficacy and tolerability of ascending doses of OPC-14597 compared to placebo and to haloperidol in acutely relapsing hospitalized schizophrenic patients.

2.Protocol No. 31-94-202: A dose ranging study of the efficacy and tolerability of OPC-14597 in acutely relapsing hospitalized schizophrenic patients.

3.Protocol No. 31-97-201: A phase III double-blind placebo-controlled study of aripiprazole in the treatment of psychosis.

4.Protocol No. 31-97-202: A phase III double-blind placebo-controlled study of aripiprazole in the treatment of psychosis, with risperidone as active control.

5.Protocol No. 31-97-203: An open-label follow-on study of the long-term safety of aripiprazole in patients with psychosis.

These adult studies were combined with the pediatric studies to compare the pharmacokinetic parameters between adults and adolescents.

Listing of Pediatric Studies.

Table 1. Studies Used for the Population Pharmacokinetic Analysis			
Protocol No.	**31-03-238**	**31-03-239**	**31-03-240**
Type of Study	PK/Tolerability	Efficacy/Safety	Efficacy/Safety
Study Design	Open Label, ascending dose	3 Arm, Randomized, Placebo controlled	3 Arm, Randomized, Placebo controlled
Dosage Regimen	2 mg – 30 mg aripiprazole once a day	10 mg or 30 mg aripiprazole once a day	10 mg or 30 mg aripiprazole once a day
No. of Subjects	21 enrolled	302 randomized	290 randomized
Study Population	Adolescents 13 - 17 years of age with schizophrenia and Children and adolescents 10-17 years of age with mania associated with bipolar disorder	Adolescents 13-17 y/o with schizophrenia	Children and adolescents 10-17 years of age with mania associated with bipolar disorder
Duration of Treatment	Up to 26 days	6 weeks	4 weeks + 6 months extension

The pharmacokinetic sample times are shown in Table 2.

Table 2. Population Pharmacokinetic Sampling Times	
Protocol No.	
31-03-238	serial samples on day 14 of the fixed dose phase at predose and 1, 2, 3, 4, 6, 8, 10, and 24 h post-dose
31-03-239	samples collected predose on Day 1 (baseline), and at any time on Days 7, 14, 21, 28, 35, and 42/Early Termination
31-03-240	samples collected predose on Day 1 and Weeks 1, 2, 3, and 4

ASSAY VALIDATION

ANALYTICAL

	Begin Clinical	End Clinical			
Study	1st PK Sample Collected	Last PK Sample Collected	Begin Anaylsis	End Analysis	Total Storage (Days)
31-03-238	19-Aug-04	8-Jun-05	3-Nov-04	18-Jul-05	333
31-03-239	6-Aug-04	28-Jul-06	14-Dec-05	17-Oct-06	802
31-03-240	4-Jan-05	24-Jul-06	19-Dec-05	31-Mar-07	816

Total duration of OPC-14597 and OPC-14857 stability at -20 degrees = 668 Days

Assay Validation - CN138016

Parameter	OPS-14597-Parent	OPC 14857-Metabolite
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection	LC\ Mass Spectrometric \ Mass Spectrometric Detection
Number of Freeze-thaw	3 Cycles	3 Cycles
Benchtop Stability at RT	24 hrs	24 hrs
Long term at –20° C	668 days *	668days
Extraction Recovery		

*The storage stability for the clinical studies was based upon the individual subjects start date and sample analysis dates. None of these exceeded 668 days.

INDIVIDUAL STUDY DETAILS

STUDY 31-03-238

OBJECTIVES

The objectives of this study were to assess the safety, tolerability, and pharmacokinetics (PK) of repeated doses of aripiprazole following oral

administration to children and adolescent patients ages 10 to 17 preferentially with a primary schizophrenia diagnosis or bipolar spectrum disorder.

METHODS

This tolerability study was a multicenter, open-label, sequential cohort, dose escalation trial of multiple doses of aripiprazole ranging from 2mg to 30 mg in twenty one patients with a primary schizophrenia spectrum diagnosis or bipolar spectrum disorder. Subjects were administered aripiprazole for up to 12 days (depending upon the maximum dose for the cohort) using a forced titration scheme to achieve one of the following dose levels: 20 mg, 25 mg, or 30 mg. Following the dose escalation phase, subjects entered the fixed dose phase and were administered the maximum dose for that cohort for 14 days. Subjects participated in PK sampling on Days 14 and 15 of the fixed-dose phase.

Seventeen subjects (81%) completed both the dose escalation and fixed-dose phases. A total of 21 patients (14 males and 7 females) of ages ranging from 10-17 years (mean 12.2 years) were enrolled in the study. Body weights ranged from 31.3 to 100 kg (mean 60.8 kg).

Blood was collected for the determination of aripiprazole plasma concentrations. Samples (4 mL) were taken on Days 14 and 15 of the fixed-dose phase at predose and at the following postdose hours: 1, 2, 3, 4, 6, 8, 10, and 24 hours.

Plasma Analysis Results

Parameter	OPS-14597-Parent	OPC 14857-Metabolite
Method	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	1 ng/mL	1 ng/mL
Linearity (Standard curve samples)	1-250 ng/mL	1-250 ng/mL
Quality Control (QC) Samples	4, 20, & 200 ng/mL	1.5, 20, & 200 ng/mL
Precision of Standards (%CV)	3.1% at 0.5 ng/ml 4.3% at 250 ng/ml	2.9% at 0.5 ng/ml 6.0% at 250 ng/ml
Precision of QC Samples (%CV)	6.55% at 4 ng/ml 5.7% at 200 ng/ml	4.8% at 1.5 ng/ml 4.3% at 200 ng/ml

Accuracy of Standards (%)	98% at 0.5 ng/ml 94% at 250 ng/ml	98% at 0.5 ng/ml 98% at 250 ng/ml
Accuracy of QC Samples (%)	-1.7 to -2.9%	3.3 to1.5%

STUDY 31-03-239

Objectives

The primary objective of this study was to determine the safety and efficacy of aripiprazole tablets administered as 10 mg QD and 30 mg QD in adolescent subjects, 13 to 17 years of age, with a DSM-IV diagnosis of schizophrenia for a total treatment period of 6-weeks.

Primary Efficacy Variables

The primary efficacy measure was the mean change from Baseline to Endpoint (Day 42) in the Positive and Negative Syndrome Scale (PANSS) Total Score.

METHODS

The 31-03-239 study was a multicenter, randomized, double-blind, placebo-controlled study to determine the safety and efficacy of aripiprazole tablets 10 mg once daily (QD) and 30 mg QD in adolescent subjects, 13-17 years of age, with a DSM-IV diagnosis of schizophrenia. The study was conducted on an outpatient basis.

Aripiprazole was titrated starting from 2 mg to the target dose in 5 days in the 10 mg treatment arm and in 11 days in the 30 mg treatment arm. Subjects remained at the assigned dose for at least 2 weeks. Subjects who experienced dose-related tolerability issues prior to study Day 25 were to be discontinued from the study. Beginning on Day 26, investigators could decrease the dose of aripiprazole for tolerability (to 5 mg QD in the 10 mg treatment arm and to 15 mg QD in the 30 mg treatment arm). A total of 101 centers from the United States, Europe and other regions were involved in this study. Bulgaria, Croatia, Romania, Russian Federation, Serbia and Montenegro, and Ukraine were included in the European region. Argentina, India, Jamaica, Mexico, South Africa, and South Korea were included in the other regions. Three hundred and seventy one patients (57% Male, 43% Female) were enrolled in the study and 302 patients were randomized including 93 patients from the U.S., 141 from Europe and 68 from other regions. One hundred patients were assigned to the aripiprazole 10 mg group, 102 patients to the aripiprazole 30 mg group, 100

patients to the placebo group. All 302 randomized patients were dosed and included in both efficacy analysis and safety analysis.

After a minimum 3-day antipsychotic washout period, only subjects who continued to meet entrance criteria (PANSS ≥ 70) at the baseline visit (Day 1) were evenly randomized to receive a double-blind medication as follows:
• Arm 1 (10 mg treatment arm): Aripiprazole 2 mg QD for 2 days, aripiprazole 5 mg QD for 2 days, and aripiprazole 10 mg QD as the target dose, starting on Day 5.
• Arm 2 (30 mg treatment arm): Aripiprazole 2 mg QD for 2 days, aripiprazole 5 mg QD for 2 days, aripiprazole 10 mg QD for 2 days, aripiprazole 15 mg QD for 2 days, aripiprazole 20 mg QD for 2 days, aripiprazole 30 mg QD as the target dose, starting on Day 11.

• Arm 3 (placebo arm): Matching placebo for aripiprazole tablets.
Aripiprazole was titrated to the target dose in 5 days in the 10 mg treatment arm and in 11 days in the 30 mg treatment arm. Subjects remained at the assigned dose for at least 2 weeks. Subjects who experienced dose-related tolerability issues prior to study Day 25 were to be discontinued from the study. Beginning on Day 26, investigators could decrease the dose of aripiprazole for tolerability (to 5 mg QD in the 10 mg treatment arm and to 15 mg QD in the 30 mg treatment arm).

Primary Efficacy Variables

The primary efficacy measure was the mean change from Baseline to Endpoint (Day 42) in the Positive and Negative Syndrome Scale (PANSS) Total Score.

Pharmacokinetic/pharmacodynamic Variables

Plasma aripiprazole and dehydro-aripiprazole concentrations were measured in plasma samples obtained prior to first-dose on Day 1 and at any time postdose on Days 7, 14, 21, 28, 35 and 42/early termination (ET).

ANALYTICAL

Parameter	OPS-14597-Parent	OPC 14857-Metabolite
Method	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL	0.5 ng/mL
Linearity (Standard curve samples)	0.5-250 ng/mL	0.5-250 ng/mL

Quality Control (QC) Samples	1.5, 20, & 200 ng/mL	1.5, 20, & 200 ng/mL
Precision of Standards (%CV)	3.2% at 0.5 ng/ml 4.4% at 250 ng/ml	2.9% at 0.5 ng/ml 4.7% at 250 ng/ml
Precision of QC Samples (%CV)	11.3% at 1.5 ng/ml 4.8% at 200 ng/ml	7.2% at 1.5 ng/ml 6.0% at 200 ng/ml
Accuracy of Standards (%)	99% at 0.5 ng/ml 98% at 250 ng/ml	100% at 0.5 ng/ml 97% at 250 ng/ml
Accuracy of QC Samples (%)	100% at 1.5 ng/ml 100% at 200 ng/ml	98% at 1.5 ng/ml 100% at 200 ng/ml

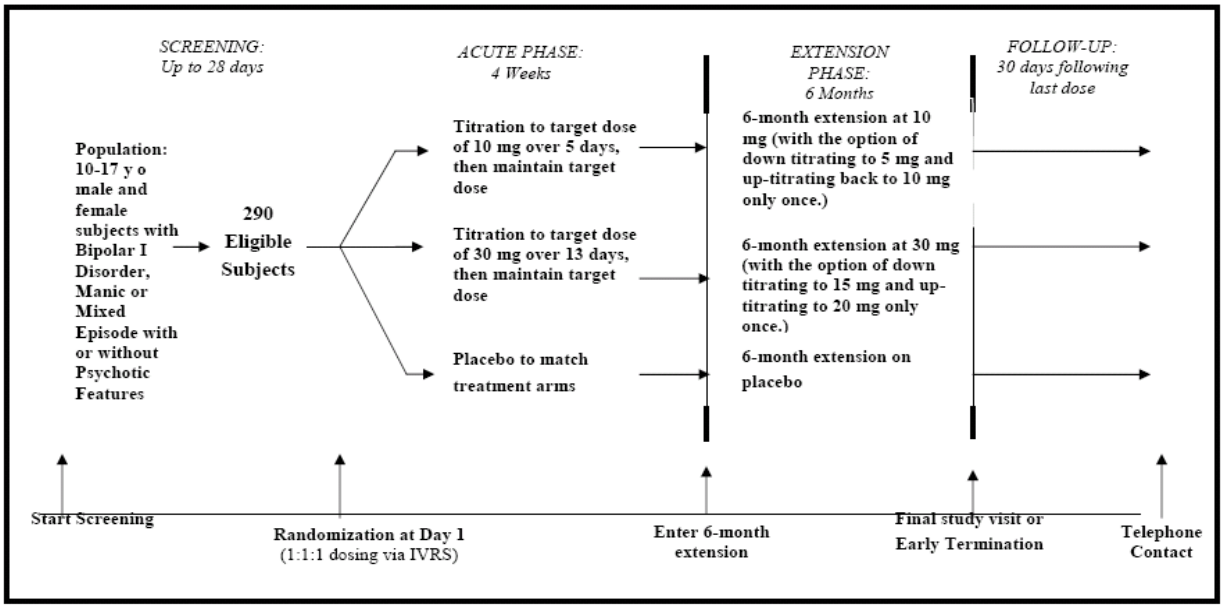
STUDY 31-03-240

OBJECTIVES:

The primary objective of this study was to compare the efficacy of two fixed doses of aripiprazole (10 mg and 30 mg) to placebo, and to assess the safety of aripiprazole in children and adolescent subjects, ages 10 to 17 years, with bipolar I disorder, manic or mixed episode with or without psychotic features. The study was designed for a total treatment period of 4 weeks in the initial Acute Phase, followed by an additional 6 months in the placebo-controlled Extension Phase.

METHODS

STUDY DESIGN SCHEMATIC



The 31-03-240 study was a multi-center, randomized, double-blind, placebo-controlled study to determine the safety and efficacy of aripiprazole tablets 10 mg once daily (QD) and 30 mg QD in pediatric patients, 10-17 years of age, with a DSM-IV diagnosis of Mania in association with Bipolar I Disorder. The study was conducted on an outpatient basis.

The primary efficacy measure for the study was the change from baseline to Week 4 (Acute Phase) on the Young Mania Rating Scale (Y-MRS) total score. The secondary efficacy measures for the Acute Phase were the following: change from baseline (to be evaluated at each visit) in the Y-MRS total score; the Children's Global Assessment Scale (CGAS) score; Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity score; the Children's Depression Rating Scale-Revised (CDRS-R) score; the General Behavior Inventory Scale (GBI) score; and the Attention Deficit Hyperactivity Disorders Rating Scale (ADHD-RS-IV) score.

Additional secondary efficacy measures were: subject response to treatment (defined as a 50% or greater reduction from baseline in Y-MRS total score); change from preceding phase score at each week on the CGI-BP; and time to discontinuations due to all reasons.

Extension Phase

The efficacy measures for the Extension Phase were the following: change from baseline (evaluated at each visit up to Week 30) in the Y-MRS total score, CGAS score, CGI-BP severity score, CDRS-R score, GBI score, and ADHD-RS-IV score. Additional efficacy measures for the Extension Phase were: subject response to treatment (defined as a 50% or higher reduction from baseline in Y-MRS total score); change from preceding phase score at each visit up to Week 30 on the CGI-BP; and time to discontinuation due to all reasons.

Pharmacokinetic/pharmacodynamic Variables

Blood sampling for population PK analysis was performed during the Acute Phase at Day 1 (Baseline), and Weeks 1, 2, 3, and 4. A 4-mL sample was obtained just prior to dosing on these days. Samples were analyzed for aripiprazole and dehydro-aripiprazole concentrations.

Safety Variables

Acute Phase
The following safety measures were evaluated for the Acute Phase:
• The frequency by severity of AEs, SAEs (clinical and laboratory), and discontinuations from the study due to adverse events through Week 4.
• Change from baseline through Week 4 on the Simpson-Angus Scale (SAS) score, Abnormal Involuntary Movement Scale (AIMS) score, and Barnes-Akathisia Rating Scale (BARS) score.
• Changes from baseline in vital sign parameters (supine and standing positions), electrocardiograms (ECGs), serum prolactin concentrations, routine laboratory tests (including creatine phosphokinase [CPK] results), and physical examination findings through Week 4.
• Percentage of subjects showing significant weight gain or loss from randomization through Week 4 (significant weight change was a ≥ 7 % increase or decrease in weight).
• Change from baseline through Week 4 in body mass index (BMI), waist circumference, blood pressure, and fasting insulin levels, triglycerides, high density lipoproteins, and glucose.

This study was designed to be conducted either on an outpatient basis or in a partial or full inpatient basis at any given time of the study. A minimum of 330 patients who met entrance criteria were anticipated to be screened for the study at approximately 60 sites in the US, with the expectation that approximately 290

subjects would be randomized to yield at least 261 (87 per treatment arm) evaluable subjects.

In the Acute Phase, subjects were screened for a period of up to 28 days (including appropriate medication washout), and if they met entrance criteria, were randomized on Day 1 to either 10 mg or 30 mg of aripiprazole or to placebo according to the following titration scheme:
• Treatment Arm 1 (10 mg treatment arm): Aripiprazole 2 mg/day for 2 days, aripiprazole 5 mg/day for 2 days, and aripiprazole 10 mg/day as the target dose starting on Day 5. Subjects remained on the 10 mg dose for the remainder of the Acute Phase treatment period.

• Treatment Arm 2 (30 mg treatment arm): Aripiprazole 2 mg/day for 2 days, aripiprazole 5 mg/day for 2 days, aripiprazole 10 mg/day for 2 days, aripiprazole 15 mg/day for 2 days, aripiprazole 20 mg/day for 2 days, aripiprazole 25 mg/day for 2 days and aripiprazole 30 mg/day as the target dose starting on Day 13. Subjects remained on the 30 mg dose for the remainder of the Acute Phase treatment period.

• Treatment Arm 3 (Placebo Arm): Matching placebo for aripiprazole tablets.

Subjects reached their target dose through a forced titration schedule and proceeded with treatment at their target dose until Week 4. If the subject reached Week 4, he or she continued into the Extension Phase, a 6-month double-blind treatment period, beginning at the same dose taken at the end of the Acute Phase.
A total of 66 centers participated from the United States. A total of 413 patients were enrolled in the study and 296 patients (54% Male, 46% Female) were randomized. Ninety-eight patients were assigned to the aripiprazole 10 mg group, 99 patients to the aripiprazole 30 mg group, 99 patients to the placebo group. Of the patients randomized in the study, all 296 patients were included in the efficacy analysis and 294 patients were dosed and included in the safety analysis.

ANALYTICAL

Parameter	OPS-14597-Parent	OPC 14857-Metabolite
Method	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL	0.5 ng/mL
Linearity (Standard curve samples)	0.5-250 ng/mL	0.5-250 ng/mL

Quality Control (QC) Samples	1.5, 20, & 200 ng/mL	1.5, 20, & 200 ng/mL
Precision of Standards (%CV)	2.4% at 0.5 ng/ml 5.3% at 250 ng/ml	3.3% at 0.5 ng/ml 5.6% at 250 ng/ml
Precision of QC Samples (%CV)	7.2% at 1.5 ng/ml 5.3% at 200 ng/ml	8.2% at 1.5 ng/ml 5.2% at 200 ng/ml
Accuracy of Standards (%)	99% at 0.5 ng/ml 99% at 250 ng/ml	99% at 0.5 ng/ml 99% at 250 ng/ml
Accuracy of QC Samples (%)	100% at 1.5 ng/ml 100% at 200 ng/ml	94% at 1.5 ng/ml 99% at 200 ng/ml

RESULTS

Table 3. Subject Disposition

Subjects	Acute Phase				Acute + Extension Phase			
	Aripiprazole 10 mg (N = 98)	Aripiprazole 30 mg (N = 99)	Placebo (N = 99)	Total (N=296)	Aripiprazole 10 mg (N = 98)	Aripiprazole 30 mg (N = 99)	Placebo (N = 99)	Total (N=296)
Screened	--	--	--	--	--	--	--	413
Randomized	98 (100.0)	99 (100.0)	99 (100.0)	296 (100.0)	98 (100.0)	99 (100.0)	99 (100.0)	296 (100.0)
Withdrawn:	14 (14.3)	22 (22.2)	23 (23.2)	59 (19.9)	64 (65.3)	77 (77.8)	87 (87.9)	228 (77.0)
Adverse Experience	4 (4.1)	7 (7.1)	1 (1.0)	12 (4.1)	9 (9.2)	19 (19.2)	2 (2.0)	30 (10.1)
Lost to follow up	3 (3.1)	3 (3.0)	5 (5.1)	11 (3.7)	5 (5.1)	5 (5.1)	11 (11.1)	21 (7.1)
Subject met withdrawal criteria	--	--	--	--	3 (3.1)	1 (1.0)	2 (2.0)	6 (2.0)
Investigator withdrew subject	1 (1.0)	0 (0.0)	2 (2.0)	3 (1.0)	5 (5.1)	8 (8.1)	7 (7.1)	20 (6.8)
Subject withdrew consent	4 (4.1)	9 (9.1)	6 (6.1)	19 (6.4)	20 (20.4)	28 (28.3)	21 (21.2)	69 (23.3)
Protocol deviation	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.7)	3 (3.1)	3 (3.0)	1 (1.0)	7 (2.4)
Lack of efficacy as determined by investigator	2 (2.0)	2 (2.0)	8 (8.1)	12 (4.1)	19 (19.4)	13 (13.1)	43 (43.4)	75 (25.3)
Efficacy ITT[a]	98 (100.0)	99 (100.0)	99 (100.0)	296 (100.0)	98 (100.0)	99 (100.0)	99 (100.0)	296 (100.0)
Completers[b]	84 (85.7)	77 (77.8)	76 (76.8)	237 (80.1)	34 (34.7)	22 (22.2)	12 (12.1)	68 (23.0)
Safety ITT[c]	98 (100.0)	99 (100.0)	97 (98.0)	294 (99.3)	98 (100.0)	99 (100.0)	97 (98.0)	294 (99.3)

[a]Efficacy ITT: Randomized subjects evaluated for at least one primary or secondary efficacy parameter

Table 4. Demographic Characteristics-All Subjects

Characteristic	Statistic	Aripiprazole 10 mg (N = 98)	Aripiprazole 30 mg (N = 99)	Placebo (N = 99)	Total (N = 296)
Age (years)	N	98	99	99	296
	Mean (SD)	13.70 (2.17)	13.31 (2.32)	13.28 (2.12)	13.43 (2.21)
	Range	10 - 17	10 - 17	10 - 17	10 - 17
Height (cm)	N	98	99	99	296
	Mean (SD)	161.05 (12.45)	158.37 (12.21)	158.69 (11.63)	159.36 (12.12)
	Range	119.0 - 190.5	127.0 - 183.0	134.1 - 189.0	119.0 - 190.5
Weight (kg)	N	98	99	99	296
	Mean (SD)	63.76 (20.11)	60.49 (21.50)	60.48 (17.31)	61.57 (19.71)
	Range	26.59 - 136.13	20.45 - 121.10	29.09 - 103.60	20.45 - 136.13
BMI	N	98	99	99	296
	Mean (SD)	24.15 (5.37)	23.66 (6.70)	23.68 (4.98)	23.83 (5.72)
	Range	14.17 - 42.02	12.68 - 43.67	14.39 - 34.94	12.68 - 43.67
Gender[a]	Male, n (%)	52 (53.06)	51 (51.52)	56 (56.57)	159 (53.72)
	Female, n (%)	46 (46.94)	48 (48.48)	43 (43.43)	137 (46.28)
Race[a]	Caucasian, n (%)	65 (66.33)	68 (68.69)	60 (60.61)	193 (65.20)
	Black, n (%)	24 (24.49)	18 (18.18)	23 (23.23)	65 (21.96)
	Native Hawaiian or Other Pacific Islander, n (%)	2 (2.04)	0 (0.00)	0 (0.00)	2 (0.68)
	Other, n (%)	7 (7.14)	13 (13.13)	16 (16.16)	36 (12.16)

Characteristic	Statistic	Aripiprazole 10 mg (N = 98)	Aripiprazole 30 mg (N = 99)	Placebo (N = 99)	Total (N = 296)
Ethnicity[a]	Hispanic/Latino, n (%)	6 (6.12)	10 (10.10)	15 (15.15)	31 (10.47)
	NonHispanic/ Latino, n (%)	92 (93.88)	89 (89.90)	84 (84.85)	265 (89.53)

[a]Percentages were based on the number of randomized subjects.

Table 5. Summary of Adverse Events

Number of:	Acute Phase				Acute + Extension Phases			
	Arip 10 mg n (%)	Arip 30 mg n (%)	Placebo n (%)	Total n (%)	Arip 10 mg n (%)	Arip 30 mg n (%)	Placebo n (%)	Total n (%)
Subjects treated, N	98	99	97	294	98	99	97	294
Subject days of drug exposure, N	2449	2363	2260	7072	10655	8608	5864	25127
Subjects with AEs	73 (74.5)	75 (75.8)	60 (61.9)	208 (70.7)	78 (79.6)	84 (84.8)	66 (68.0)	228 (77.6)
AEs, N	282	357	172	811	493	476	216	1185
Subjects with TEAEs	72 (73.5)	75 (75.8)	57 (58.8)	204 (69.4)	78 (79.6)	84 (84.8)	64 (66.0)	226 (76.9)
TEAEs, N	256	326	156	738	376	366	164	906
Subjects with serious TEAEs	5 (5.1)	2 (2.0)	5 (5.2)	12 (4.1)	5 (5.1)	7 (7.1)	6 (6.2)	18 (6.1)
Subjects with severe TEAEs	6 (6.1)	5 (5.1)	4 (4.1)	15 (5.1)	9 (9.2)	9 (9.1)	5 (5.2)	23 (7.8)
Subjects discontinued study medication due to AEs	6 (6.1)	8 (8.1)	2 (2.1)	16 (5.4)	9 (9.2)	19 (19.2)	2 (2.1)	30 (10.2)

Arip = Aripiprazole

FIRM'S POPULATION PK ANALYSIS

Base Pharmacokinetic Model

A one-compartment model parameterized in terms of CL/F, V/F, and KA with interindividual variability terms on each parameter was selected based on survey of the data available in the PK database and a previous population analysis in adults.

Final Pharmacokinetic Model

Models with both size independent and allometrically scaled CL/F and V/F parameters were investigated, and a number of size metrics were evaluated including Lean Body Weight (LBW), Body Mass Index (BMI), Body Surface Area (BSA), and Body Weight. An allometric model and fixed power parameters of 0.75 for CL/F and 1.0 for V/F were applied, the median value of the size metric in the PK database or standard reference weights (i.e. 70 kg for body weight) were used.
A number of size metrics were evaluated and calculated as shown below.

Body surface area (BSA) using the method of Gehan and George([1]):

$$BSA(m^2) = 0.024265 \cdot Weight(kg)^{0.51456} \cdot Height(cm)^{0.42246} \quad (1)$$

Body mass index (BMI) as reported by Stevens et al.([2]):

$$BMI(kg/m^2) = \frac{Weight(kg)}{Height(m)^2}. \quad (2)$$

Lean body mass (LBM) as:

$$LBM(kg) = 1.10 \cdot Weight(kg) - \frac{128 \cdot Weight(kg)^2}{Height(cm)^2} \text{ in males} \quad (3)$$

$$LBM(kg) = 1.07 \cdot Weight(kg) - \frac{148 \cdot Weight(kg)^2}{Height(cm)^2} \text{ in females.} \quad (4)$$

$$TVP = \theta_{TVP} \cdot \left(\frac{WT_i}{WT_{ref}} \right)^{\theta_{allo}} \quad \text{(Eq. 5)}$$

where: the typical value of a model parameter (TVP) was described as a function of individual body weight (WTi), normalized by a reference weight (WTref), which was the median weight (61 kg) or 70 kg. θ_{TVP} is an estimated parameter describing the typical PK parameter value for an individual with weight equal to the reference weight and θ_{allo} is a fixed allometric power parameter, which was assigned a value of 0.75 for CL/F and a value of 1 for V/F. (Eq. 5)

Random effects were assumed to be parametrically distributed. As a starting point for this analysis, all inter-individual error terms were described by an exponential error model, or log-normal parameter distribution (Eq. 6). A full block covariance matrix was used for the inter-individual random effects.

$$P_i = \hat{P}\exp(\eta_{Pi}) \quad \text{(Eq. 6)}$$

where:

Pi is the estimated parameter value for individual i

$\hat{P}$ is the typical population value (geometric mean) of the parameter

η_{Pi} are individual-specific inter-individual random effects for individual i and parameter P and are assumed to be distributed: η~N(0, ω2) with covariances defined by the inter-individual covariance matrix Ω.

For PK observations in this analysis, the residual error model initially was described by a combined additive and proportional error model (Eq 7).

$$C_{ij} = \hat{C}_{ij}(1+\varepsilon_{pij}) + \varepsilon_{aij} \quad \text{(Eq. 7)}$$

where:

Cij is the jth measured observation in individual i

εpij and εaij are proportional and additive residual random errors, respectively, for individual i and measurement j and are each assumed to be independently and identically distributed: ε~NID(0, σ2).

Model selection was driven by the data and based on various goodness-of-fit criteria: (i) visual inspection of diagnostic scatter plots (observed vs. predicted concentration).

The final model was parameterized with lean body weight as a covariate on CL/F and total body weight as a covariate on V/F.

Non-parametric Bootstrap

Estimates of the precision of PK model parameters (bootstrap 95% CIs) were provided for each of the parameters. The precision of model parameters were investigated by performing a stratified non-parametric bootstrap procedure. One thousand replicate datasets were generated by random sampling with replacement using the individual as the sampling unit. Stratification by weight during the random sampling process was implemented to ensure that the bootstrap datasets adequately represented the original data with respect to body size. Population parameters for each dataset were estimated using NONMEM and the final PK model. This resulted in a distribution of approximately 1000 estimates for each population model parameter. Empirical 95% CIs were

constructed by observing the 2.5th and 97.5th quantiles of the resulting parameter distributions for those bootstrap runs that provided a result.

Posterior Predictive Check

The adequacy of the final PK model and parameter estimates was investigated with a posterior predictive check. The posterior predictive check takes into account parameter uncertainty and inter-individual and residual variance. Parameter uncertainty is taken into account by using the parameter estimates (fixed and random) from the bootstrap runs to simulate data based on the original dataset and associated covariates. Each bootstrap run provides a set of parameters for simulation. The distribution of the mean concentration (Cavg) of the simulated data was compared with the distribution of the same characteristic in the observed dataset, using exploratory graphics (quantile–quantile plots and histograms).

Predictive Check

The adequacy of the final PK model and parameter estimates was investigated with a predictive check method. This is similar to the previously described posterior predictive check, but assumes that parameter uncertainty was negligible, relative to inter-individual and residual variance. The basic premise is that a model and parameters derived from an observed dataset should produce simulated data that are similar to the original observed data. The predictive check is a useful adjunct to typical diagnostic plots, in that the predictive check provides information about the performance of random effects parameter estimates; whereas typical diagnostic plots are primarily informative about the fixed effects parameter estimates. One hundred Monte Carlo simulation replicates of the original dataset were generated using the final population PK model. The distribution of the mean concentration (Cavg) of the simulated data was compared with the distribution of the same characteristic in the observed dataset, using exploratory graphics (quantile–quantile plots and histograms).

FIRM'S RESULTS

Table 6.Patient and PK Sample Accounting

Study	238			239		240		All Studies			Total
Dose Group	20	25	30	10	30	10	30	10	20-25	30	All
#Patients Randomized	8	7	6	100	102	98	99	206	15	207	428
#Patients with PK[b]	7	5	6	76	78	85	86	161	12	170	343
#Samples in PK Database	54	45	54	367	384	269	271	636	99	709	1444
Total #Samples	54	45	54	625	616	414	418	1039	99	1088	2226
#(%) Samples Excluded	0	0	0	258 (41)	232 (38)	145 (35)	147 (35)	403 (39)	0	329 (35)	782 (35)

[a] The counts exclude patients randomized to placebo

[b] The number of samples per patient are presented in PKE 2

Typical population PK parameters (95% CI) given the reference covariates (70 kg weight and 50 kg lean body mass) were 3.44 (3.26, 3.63) L/hr, 255 (231, 283) L, and 1.67 (0.748, 4.28) hr -1 for CL/F, V/F, and ka, respectively (Tables 7 and Table 8 give the base and final model parameters).

Table 7. Pediatric Base Model

Parameter	CL	V	Ka
THETA	3.13 L/hr	231 L	0.398 hr-1
ETASD	0.440454	0.679706	2.35584
THETA:se%	0.5	14.3	0.7
OMEGA :se%	0.4	0.5	0.4
RESIDUAL ESTIMATES			
ERRSD1	19.49		
ERRSD2	0.18		
SIGMA:se%	12.2	0.4	

Table 8. Pediatric Final Model

Parameter	Parameter estimate[b]	%RSE[a]	95% Confidence interval[b]		CV%
			Lower bound	Upper bound	
THETA					
CL/F	3.44	2.76%	3.26	3.63	
V/F	255	4.98%	231	283	
ka	1.67	25.5%	0.748	4.28	
OMEGA					
ω^2CL (1,1)	0.208	12.1%	0.164	0.260	45.6%
ω^2V,CL(2,1)	0.051	64.1%	-0.011	0.117*	
ω^2V(2,2)	0.199	34.9%	0.048	0.382	44.6%
ω^2Ka,CL(3,1)	-0.038	215%	-0.240	0.155*	
ω^2Ka,V(3,2)	0.315	35.1%	-0.070	0.691	
ω^2Ka(3,3)	2.57	36.9%	0.365	12	160%
SIGMA					
1,1	319	23.3%	177	494	17.8 (SD)
2,2	0.0481	16.3%	0.033	0.063	21.9%

*Indicates 95% confidence interval that includes zero

a %RSE is percent relative standard error (100% x SE/EST)

b Estimates based on Bootstrap (PKT-5)

An objective of the firm's analysis was to compare the current pediatric data with historical data previously collected in adults with schizophrenia. The study was done in 694 subjects from 5 studies. Studies were placebo controlled and open label. Adult model reported that CL was related to lean body weight.

ADULT DATA ANALYSIS

Table 9. Adult Final Data

Parameter estimates of the base pharmacokinetic model (Run 15)[a]			
Parameter	**Estimate**	**%RSE[b]**	**%CV**
CL (L/h)	3.22	2.42%	
V (L)	303	4.22%	
KA (1/h)	1.37	16.7%	
Inter-individual variability			
ω2CL	0.210	7.71%	45.8%
ω2V	0.334	19.4%	57.8%
ω2KA	1.2	77.8%	110%
Random Residual Error			
σ2P	0.0307	9.51%	17.5%

Parameter estimates of the final pharmacokinetic model (Run 262)[a]					
Parameter	**Parameter estimate**	**%RSE[b]**	**95% Confidence interval**		**CV%**
			Lower bound	**Upper bound**	
CL0	3.81	2.70%	3.61	4.01	
CLLBW	0.498	25.9%	0.245	0.751	
V0	293	3.45%	273	313	
VAGE	0.309	28.3%	0.138	0.480	
VWT	0.754	11.7%	0.581	0.927	
KA	1.06	12.2%	0.807	1.31	
Inter-individual variability					
ω2CL	0.225	7.96%	0.190	0.260	47.4%
ω2V	0.159	18.8%	0.100	0.218	39.9%
ω2KA	1.43	77.6%	0	3.61	120%
Residual variability					
σ2P	0.0302	9.50%	0.0246	0.0358	17.4%

[a] Results from Population Pharmacokinetics/Pharmacodynamics of Apripipazole, Protocol 31-00-233, Appendix 1

[b] %RSE is percent relative standard error (100% x SE/EST)

Role of Covariates

The relationship between random effects and age or body weight are shown in the following figures.

Age and Body Weight as Random Effects-Base Model

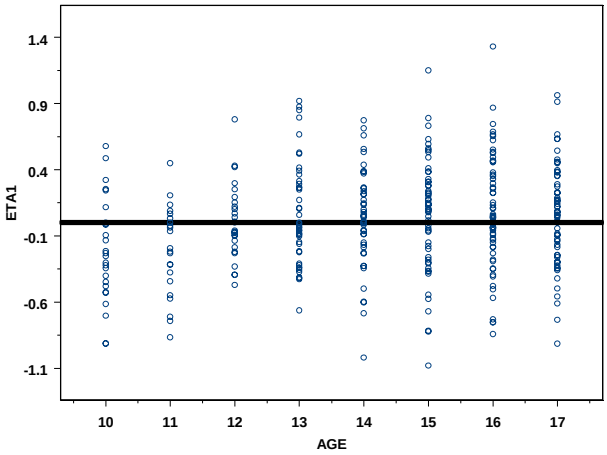


Figure 1. Relationship between eta1(random effects on CL) and age in the base model.

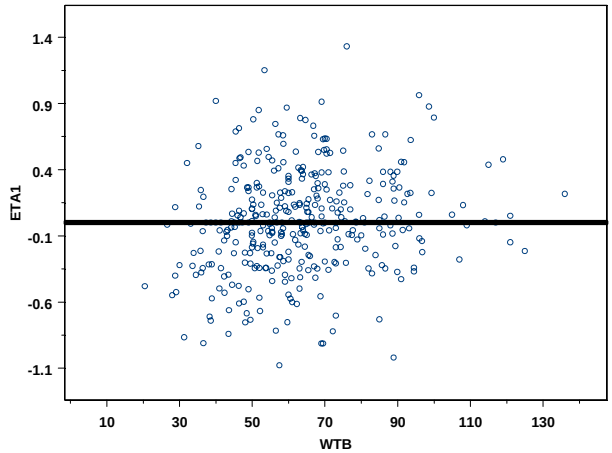


Figure 2.Relationship between eta1 (random effects on CL)and total body weight in the base model

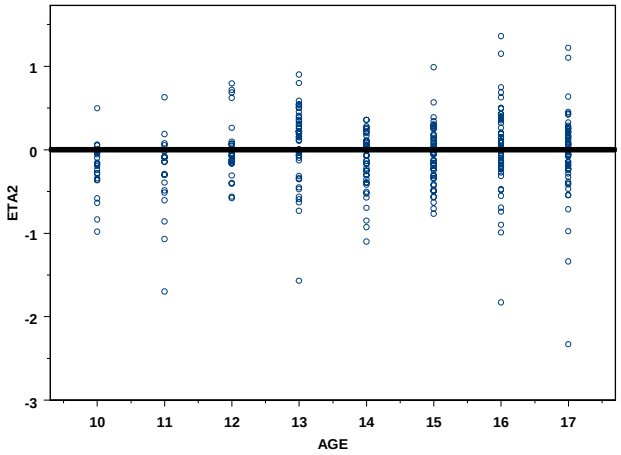


Figure 3.Relationship between eta2 (random effects on V)and age in the base model

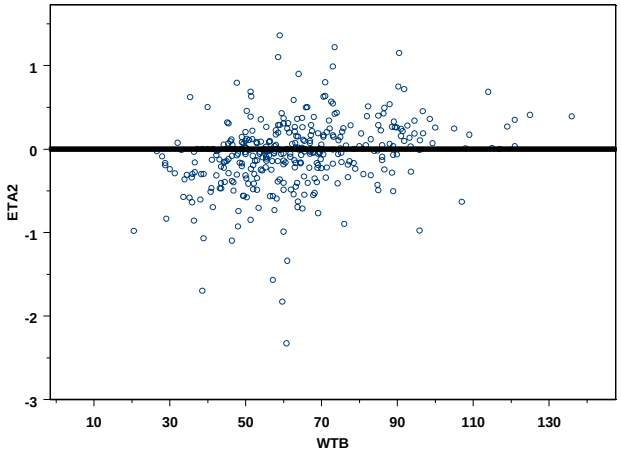


Figure 4.Relationship between eta2 (random effects on V)and total body weight in the base model.

Quality of the Data Fits-Final Model

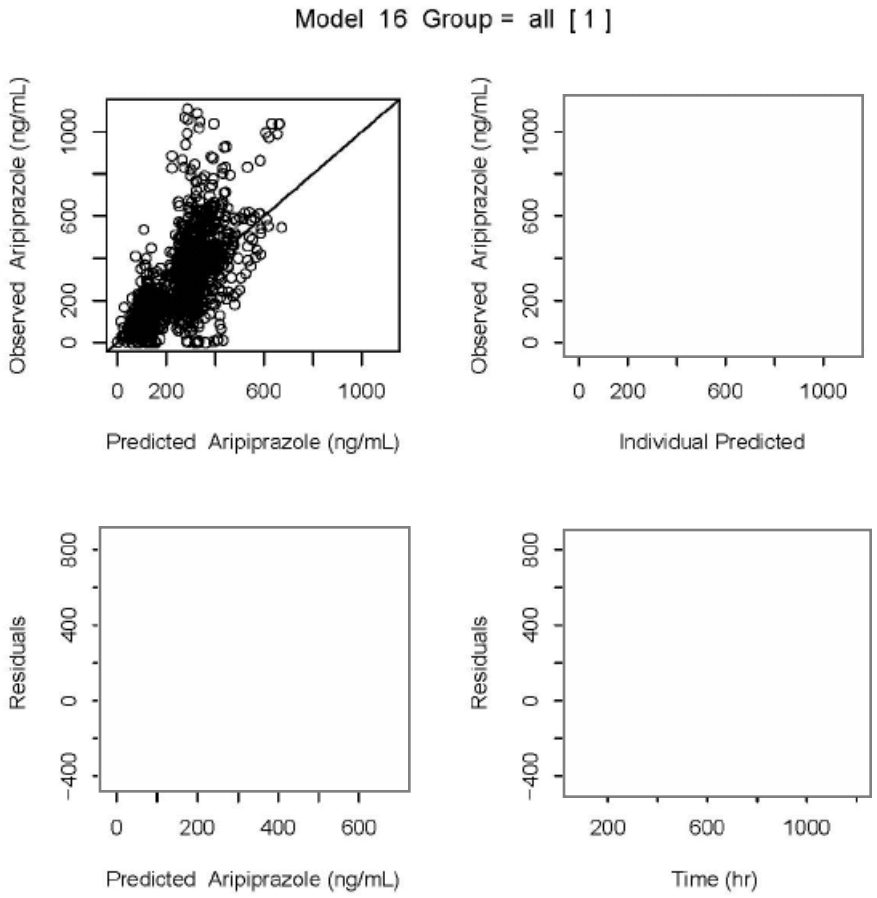


Figure 5. Observed vs Predicted and Residuals vs Conc or Time

Posterior Predictive Check and Predictive Check

Histograms of the simulated Cavg relative to the observed data for the first and third quartiles and the median are shown in figure 6 (posterior predictive check) and figure 9 (predictive check).

Simulated average steady-state trough concentrations versus observed concentrations are presented in Figure 7 (posterior predictive check) and Figure 8 (predictive check).

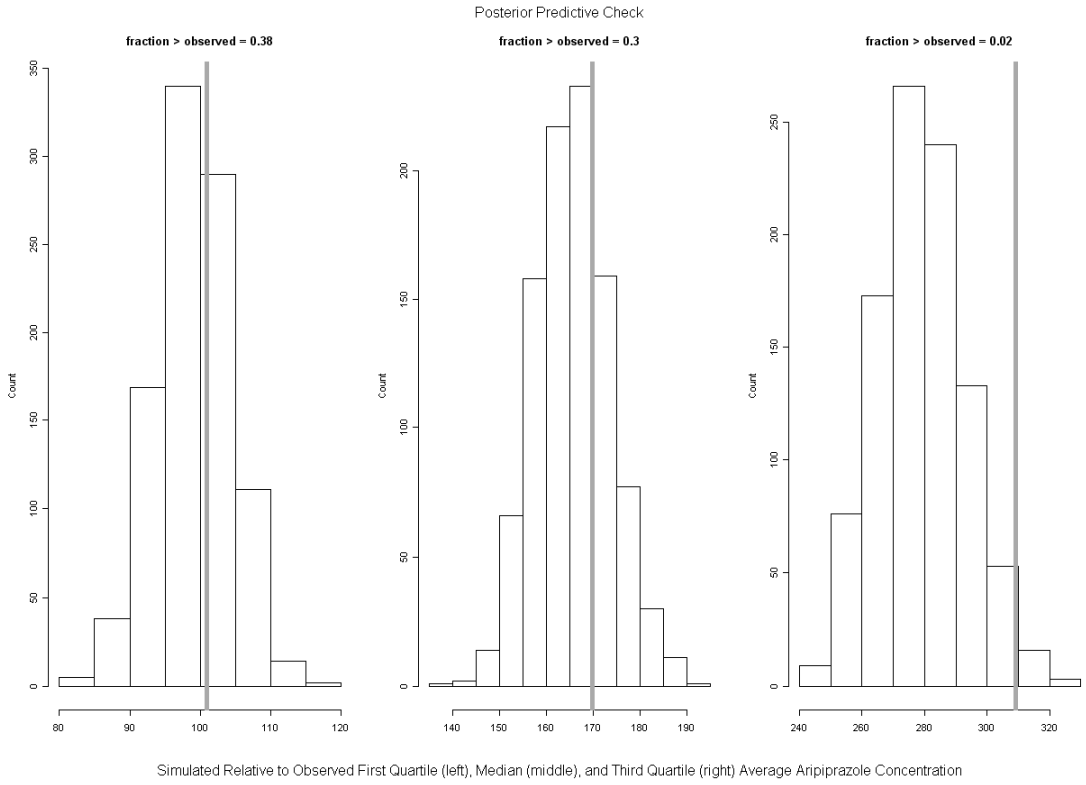


Figure 6.Posterior Predictive Check: Median and first and Last Quartile of Simulated and Observed Concentrations.

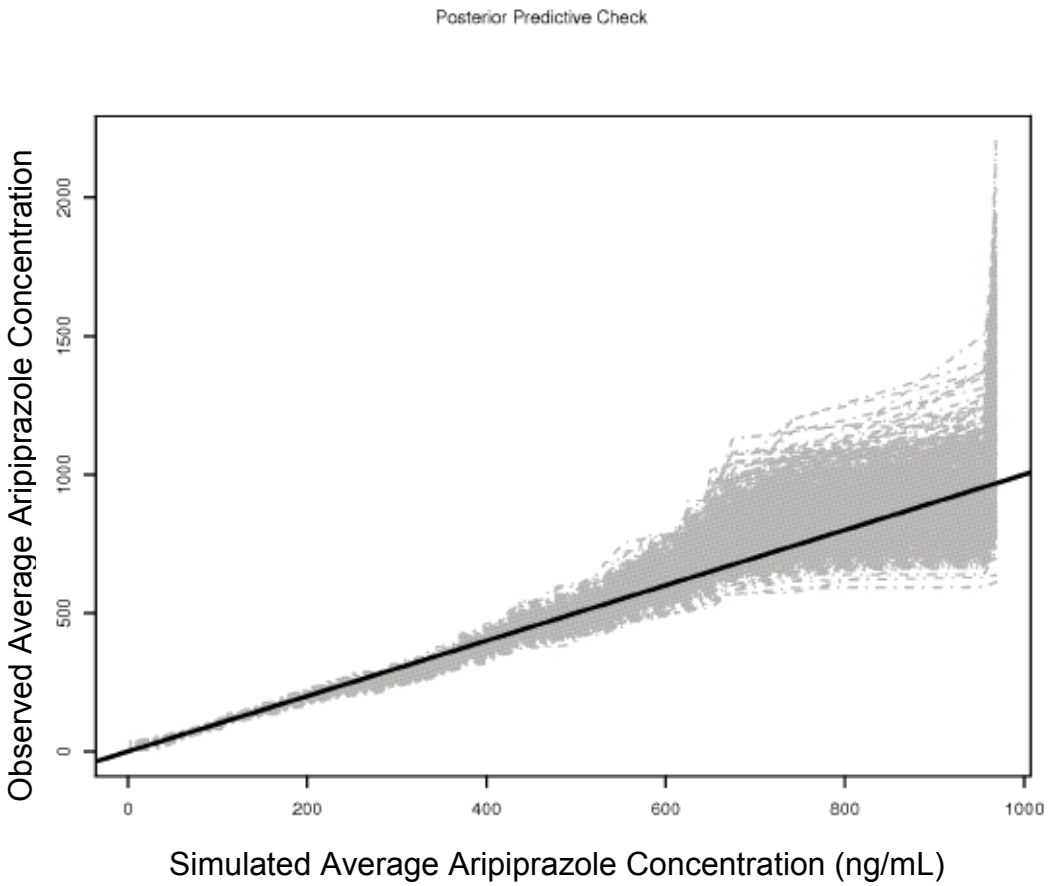


Figure 7 –Posterior Predictive Check of Observed vs Simulated Average Steady-State Trough Concentrations. The solid line is the line of identity.

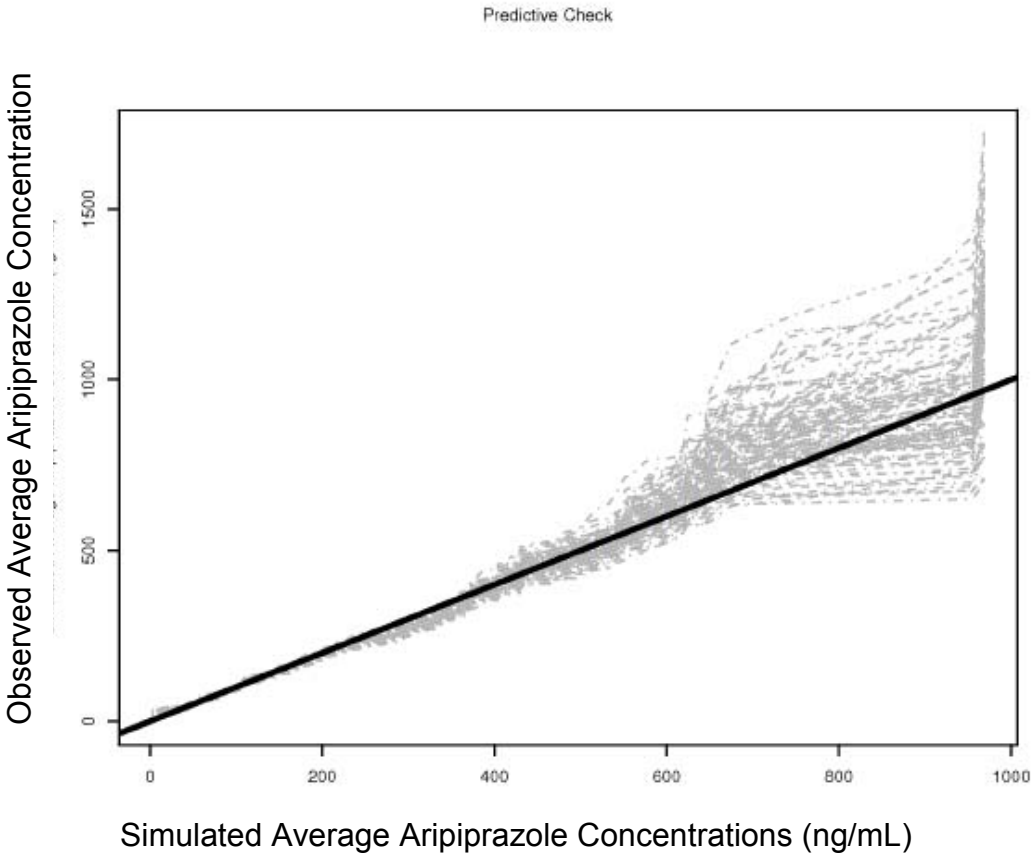
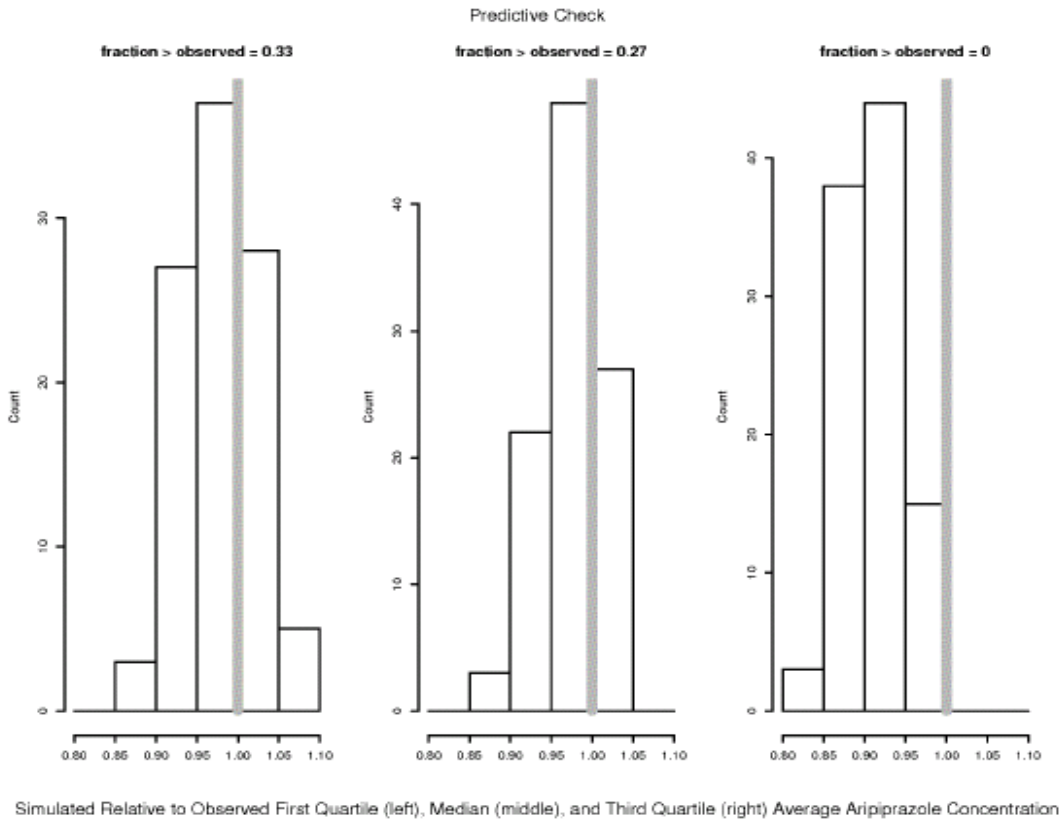


Figure 8 – Predictive Check of Observed vs Simulated Average Steady-State Trough Concentrations. The solid line is the line of identity.



Simulated Relative to Observed First Quartile (left), Median (middle), and Third Quartile (right) Average Aripiprazole Concentration

Figure 9 –Posterior Predictive Check: Median and first and Last Quartile of Simulated and Observed Concentrations.

REVIEWER'S COMMENTS

Discussion of Fitting:

1.The firm supplied the following Table 10 which summarizes the quantiles for the fitted and simulated values. It is apparent that the experimental values are underestimated for about 25-30% of the data between the 50th and 75th quantiles. The major impact would be to underestimate Cmax for study 238 (intensive sampling) and plasma levels in study 239. The underprediction would not have a major impact on study 240 since there were only 22 samples above 600 ng/ml (i.e., where the most underpredictions occurred).

Table 10. Summary Statistics of the Patient Level Mean Concentration for the Observed and Simulated Data

Quantiles of Observed and Simulated Average Concentration										
	1%	2.5%	10%	25%	50%	75%	95%	97.5%	99%	max
obs	24.8	40.4	51.8	100.5	169.7	309.3	532.7	604.9	674.4	968.3
sim	29.1	39.8	50.0	98.6	165.3	282.4	523.6	627.6	784.2	1720.7

obs = Observed data
sim = Simulated data

2.The objective function and standard deviations for the models were:

Model	No Covariates	Covariates
Objective function	13714	13561
EtaSD CL	0.44	0.459
EtaSD V	0.67	0.439

The results clearly show that although there was a significant decrease in the objective function and the intersubject variability for Volume that this had little physiological importance. This is further supported by Figures 1-4 (presented under the base model) showing the effects of age and weight on the random effects. The results in Figures 2 and 4 were interpreted by the firm to indicate a relationship between CL and total body weight up to 70 kg in weight which was impacted by including a covariate for weight in the model as evidence by the relationship in their final model. This is clearly not supported by the final relationships since the data for eta1 vs. weight in the final model was similar to that seen for the base model (Figure 10).

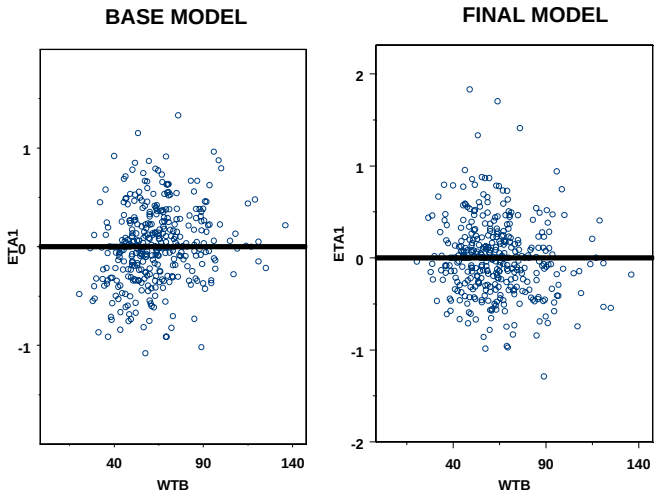


Figure 10. Relationship between total body weight and the random effects on CL with total body weight as a covariate in the base and final pharmacokinetic model.

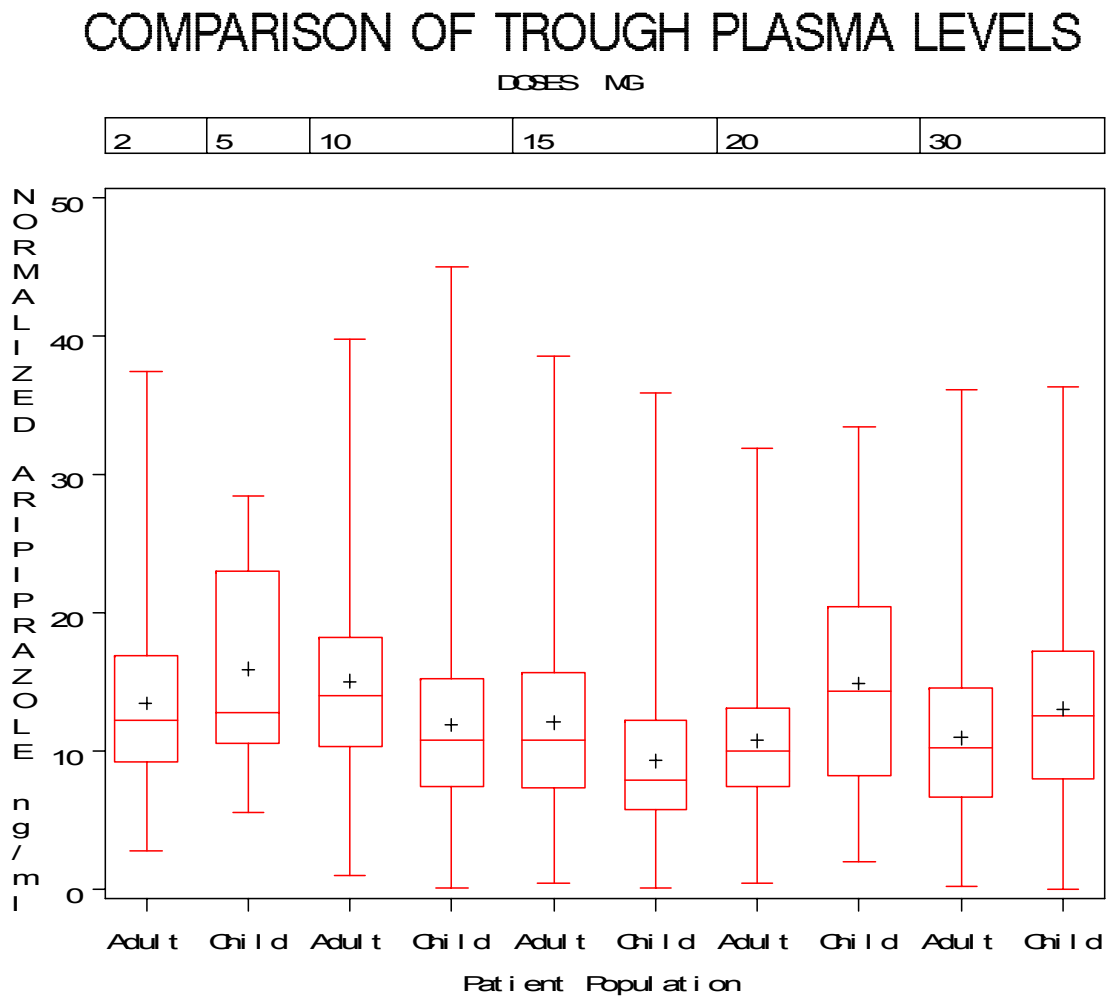


Figure 11.Dose normalized aripiprazole plasma concentrations. Subject mean weights were 82 kg for adults and 63 kg for children.

The graph indicates comparable exposure when the plasma values are dose normalized.

Plot of the plasma levels in children above and below the median weight of 61 kg also indicates that that there are no differences in exposure.

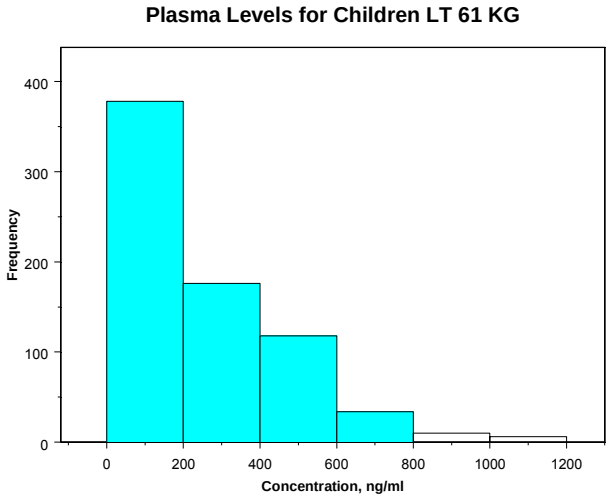


Figure 12.Plasma levels from the pop pk study for children less than the median weight of 61 kg.

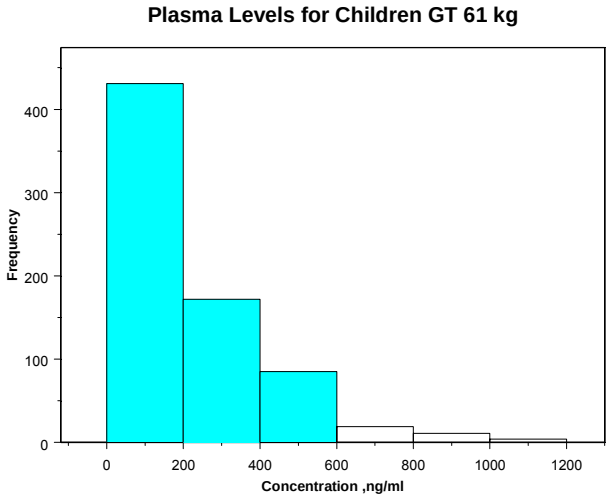


Figure 13.Plasma levels from the pop pk study for children greater than the median weight of 61 kg.

DOSE/EXPOSURE-EFFECTIVENESS RELATIONSHIP-SCHIZOPHRENIA

The relationship between effect and exposure to aripiprazole was examined.

The overall drop-out pattern was investigated between the treatments.

Drop-out pattern

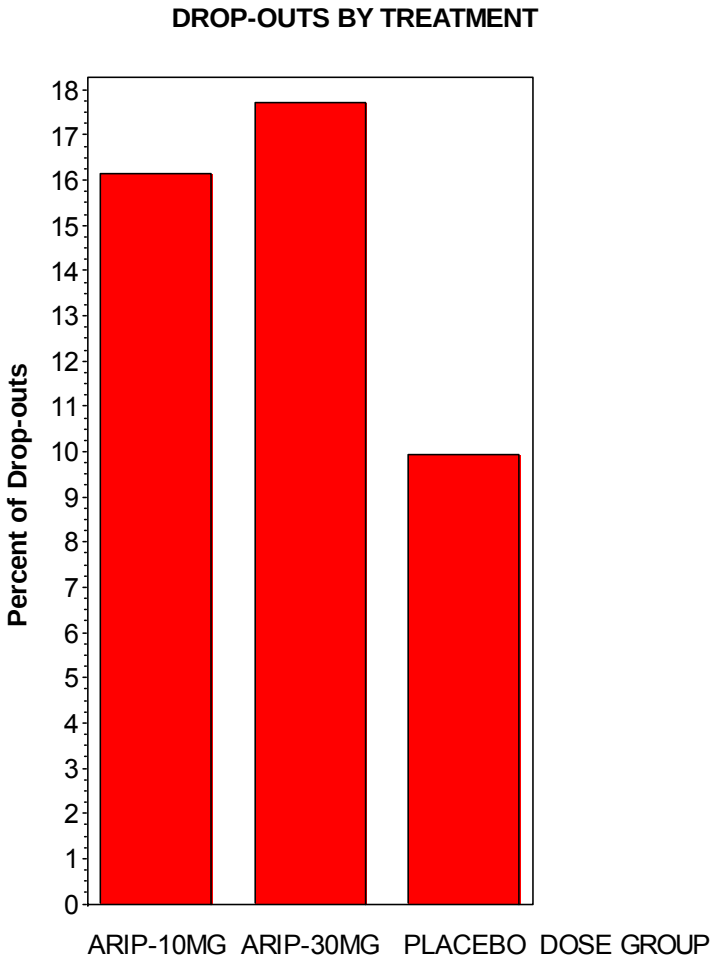


Figure 14. Total Percent of subjects that dropped out from each treatment group based upon randomized intent to treat subjects for each group.

Subject dropout pattern based upon visit day is presented in Figure 15.

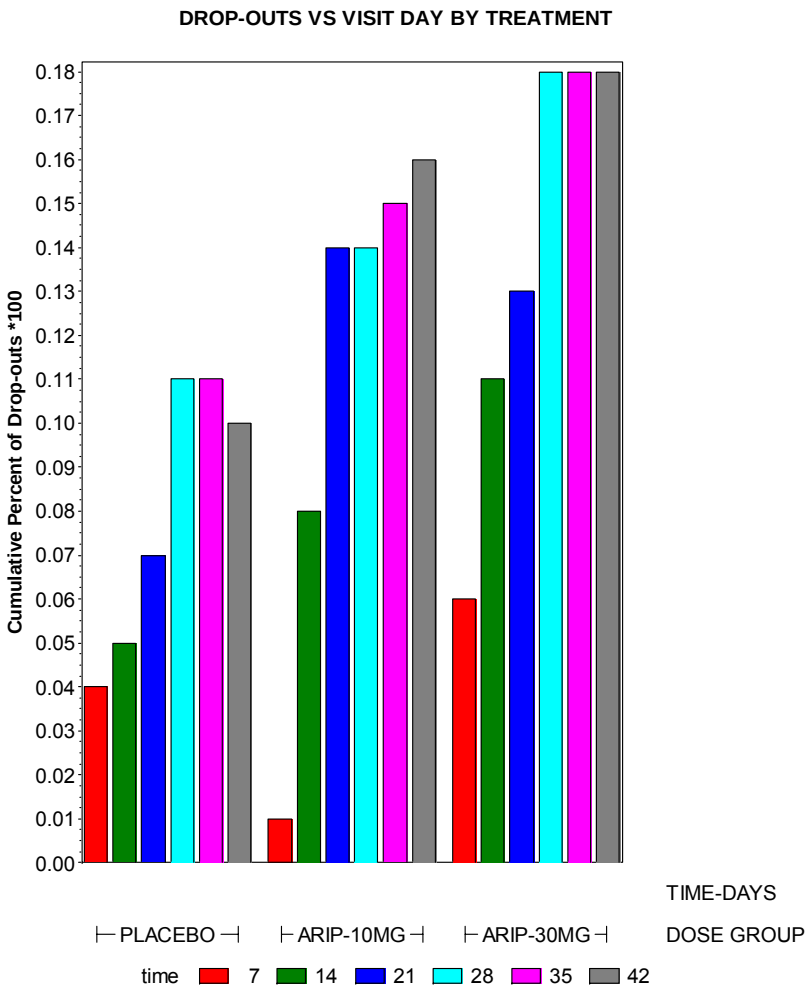


Figure 15 .Cumulative percent subject drop-outs for the placebo, 10 mg and 30 mg treatment groups as a function of treatment day. One subject that missed day 35 dosing returned for day 42 in the placebo group.

Subject drop-out pattern for the different age groups is presented in Figure 16.

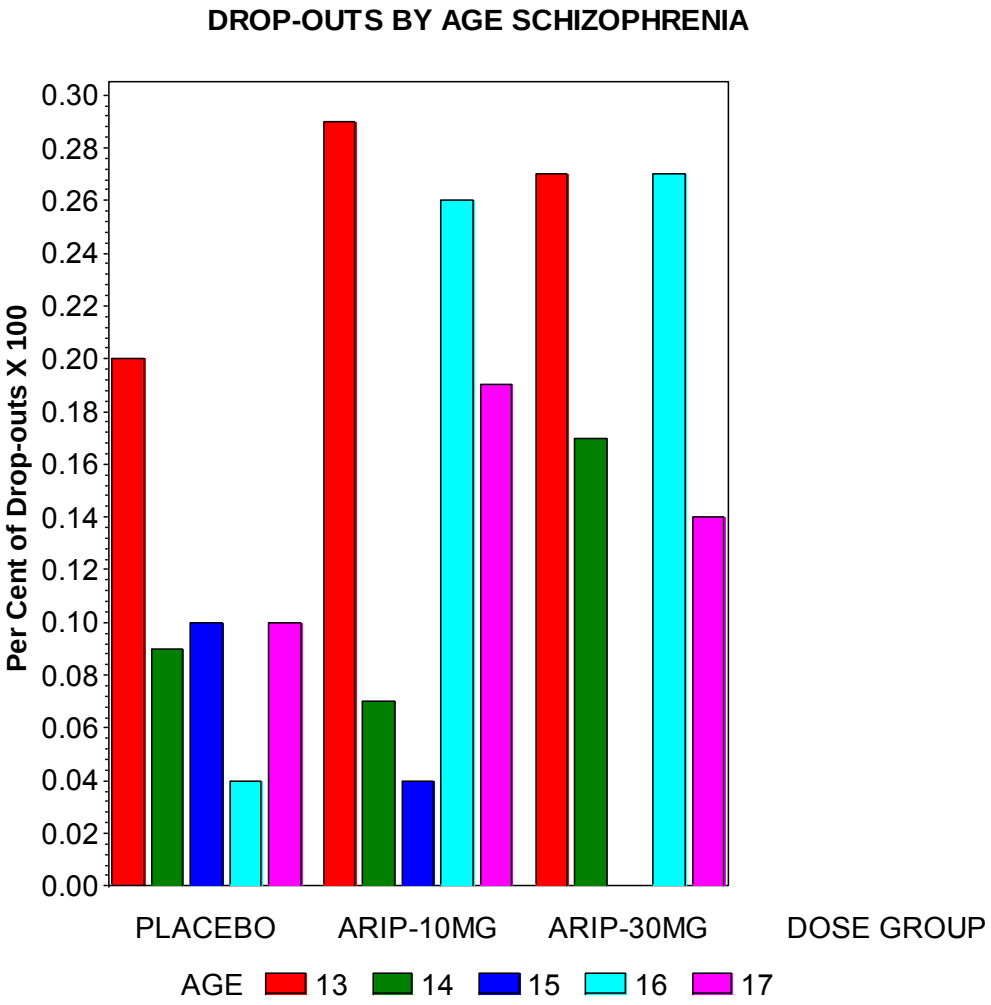


Figure 16. Per cent of dropouts per treatment group by age indicating a slightly higher per cent of drop outs for the 13 yr and 16 yr old age groups. Other age groups had comparable percentage of dropouts.

Table 11. Main reasons for drop-outs in the population as a function of dose.

Dose Group	Reason	Number	Percent of Total Subjects Randomized N=100-10mg N=102-30mg

			N=100-Placebo
10 mg	Adverse Event	7	7
	Withdrew	4	4
	Lack of efficacy	5	5
30 mg	Adverse Event	4	3.9
	Withdrew	12	11.8
	Protocol Deviation	1	0.9
	Lack of efficacy	1	0.9
Placebo	Lost to follow up	1	1
	Adverse Event	2	2
	Withdrew	5	5
	Protocol Deviation	1	1
	Lack of efficacy	1	1

The overall per cent of dropouts was higher for the higher dose (N=18 subjects).

Longitudinal data analysis

Longitudinal analysis of the exposure for all subjects is presented in Figure 17.

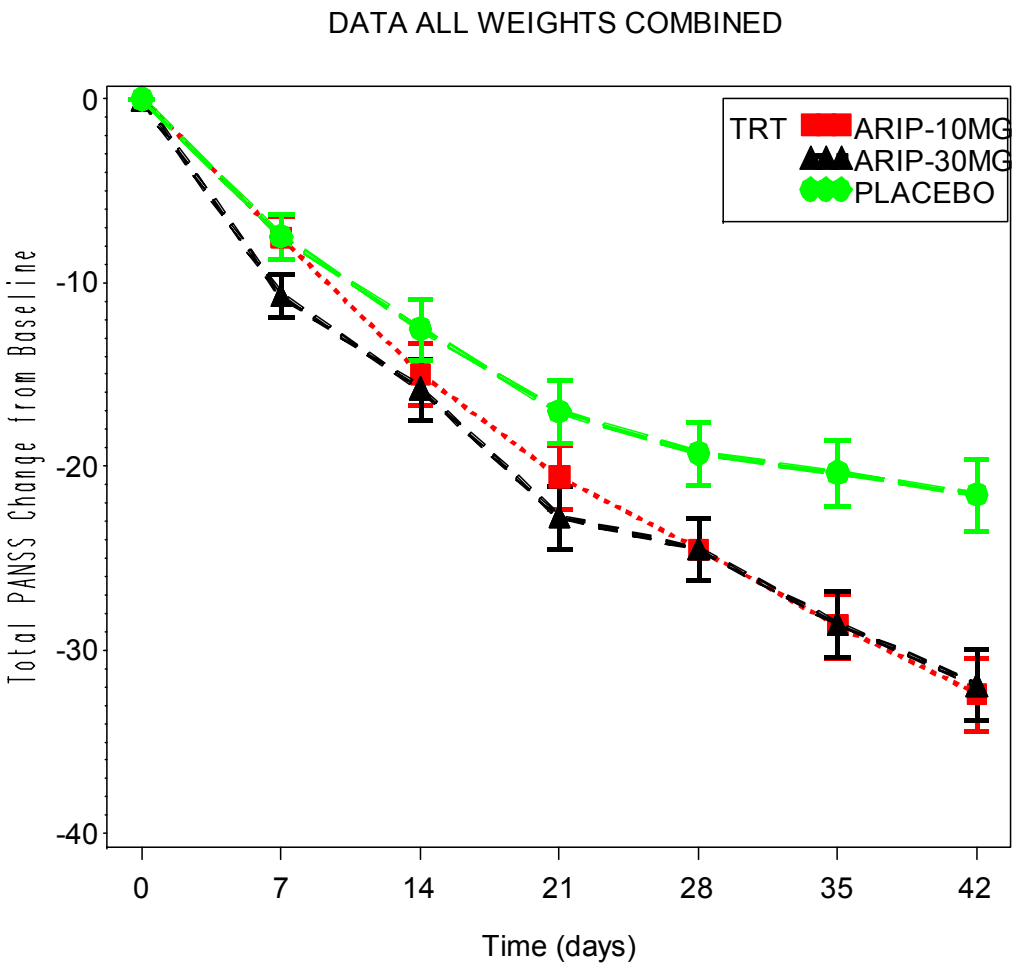


Figure 17. Analysis of PANNS scores as a function of time with all children data combined. Values are mean ± SE. Values are based upon LOCF.

ADVERSE EFFECTS

Table 12. Most Severe Reported Treatment-emergent Adverse Events with a 5% or Greater Incidence in Any Treatment Group			
Adverse Event	Aripiprazole 10 mg (N = 100) n (%)	Aripiprazole 30 mg (N = 102) n (%)	Aripiprazole Placebo (N = 100) n (%)

Somnolence	11(11%)	22(21.6%)	6(6%)
Extrapyramidal Disorder	13(13%)	22(21.6%)	5(5%)

The percent of occurrence of the main adverse effects, somnolence and extrapyrimidal effects, appeared to be dose related for the children with schizophrenia. This may explain the larger per cent of drop outs at the highest dose.

DOSE/EXPOSURE-EFFECTIVENESS RELATIONSHIP-BIPOLAR

An analysis of the bipolar data similar to that for schizophrenia was conducted to determine exposure response.

Drop-out pattern

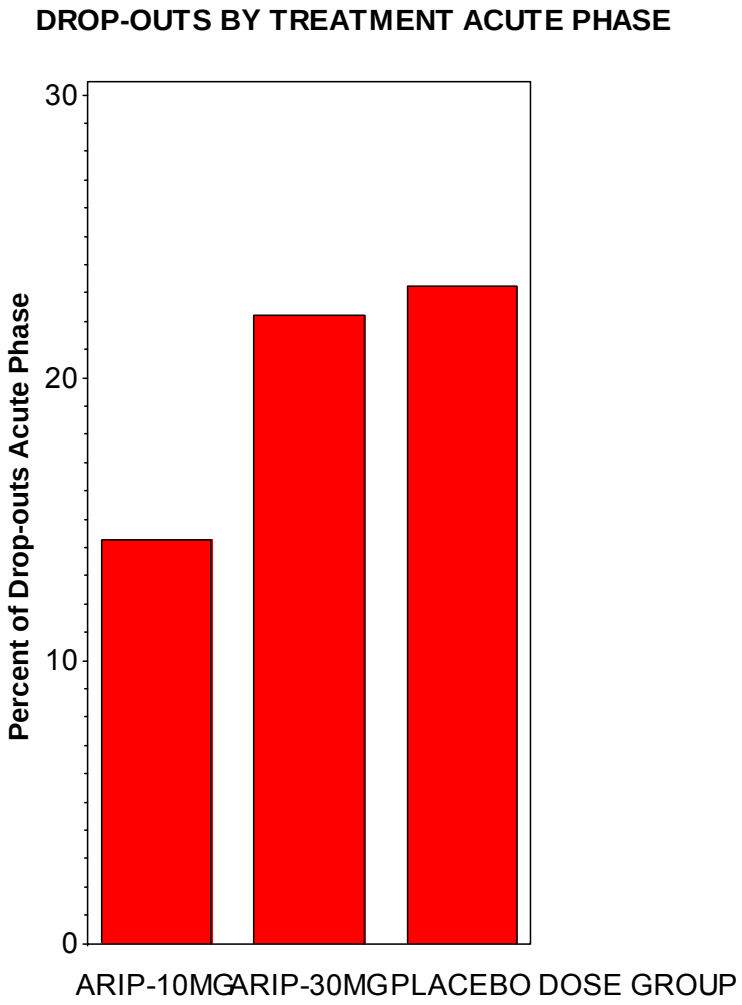


Figure 18. Total Percent of subjects that dropped out from each treatment group based upon randomized intent to treat subjects for each group.

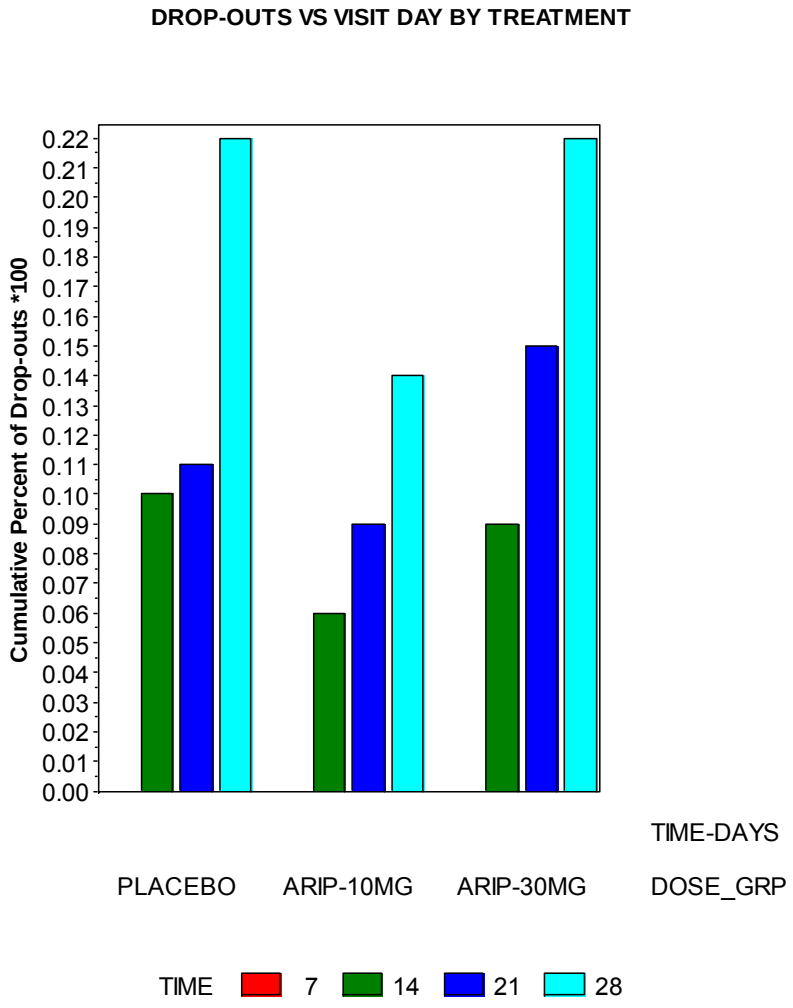


Figure 19 .Cumulative percent subject drop-outs for the placebo, 10 mg and 30 mg treatment groups as function of treatment day.

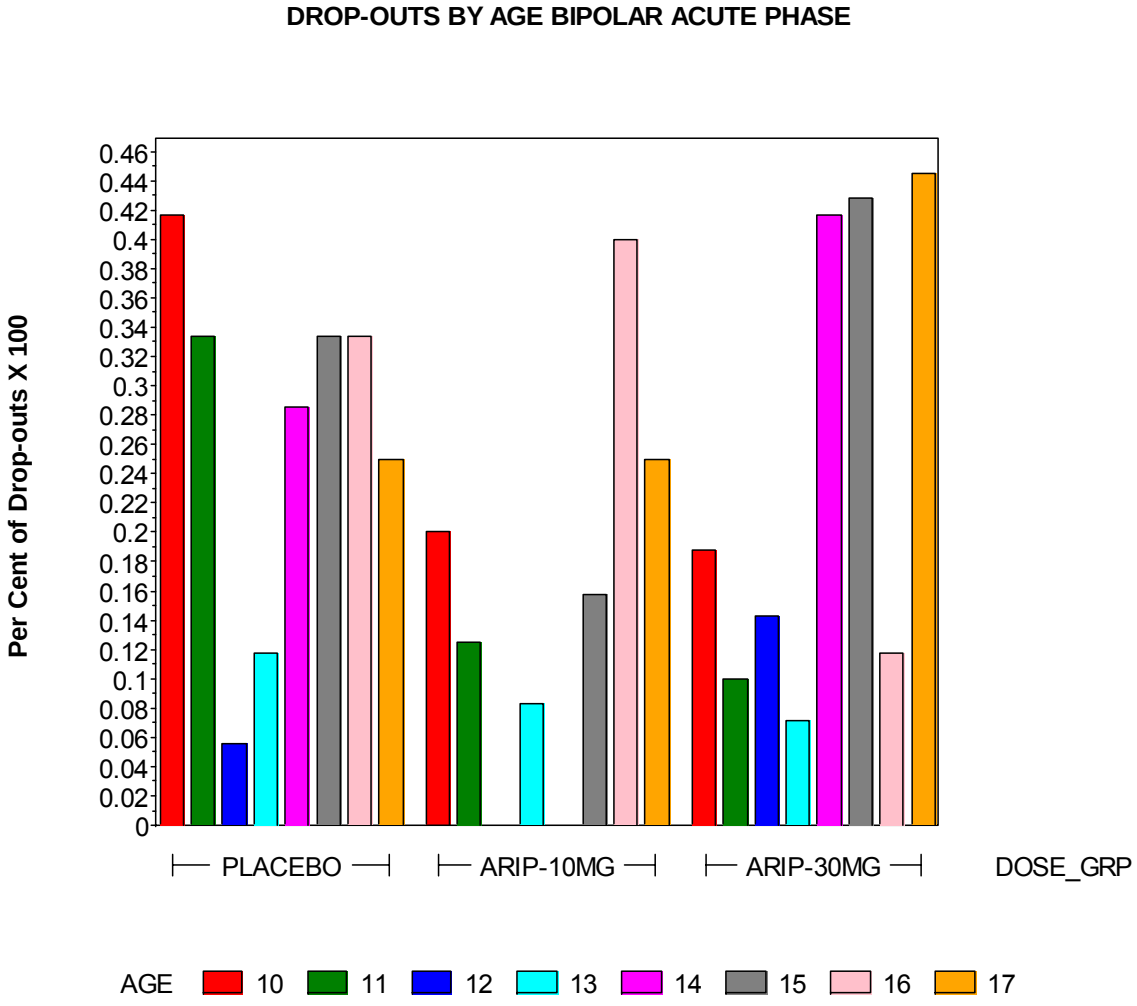


Figure 20. Per cent of drop outs by age indicating similar drop out rates for all ages.

Table 13. Main adverse events for drop-outs in the population as a function of dose in the acute study phase.

CT-8.5.1.2
Incidence of Serious Treatment-emergent Adverse Events by System Organ Class - Acute Phase

SYSTEM ORGAN CLASS	ARIP-10MG (N=98) n	(%)	ARIP-30MG (N=99) n	(%)	PLACEBO (N=97) n	(%)	TOTAL (N=294) n	(%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	(1.0)	0	(0.0)	0	(0.0)	1	(0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1	(1.0)	0	(0.0)	0	(0.0)	1	(0.3)
NERVOUS SYSTEM DISORDERS	1	(1.0)	0	(0.0)	0	(0.0)	1	(0.3)
PSYCHIATRIC DISORDERS	4	(4.1)	2	(2.0)	5	(5.2)	11	(3.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	(1.0)	0	(0.0)	0	(0.0)	1	(0.3)
TOTAL[1]	5	(5.1)	2	(2.0)	5	(5.2)	12	(4.1)

Longitudinal data analysis

The YMRS scores were analyzed in the study as a function of time for all subjects in Figure 21.

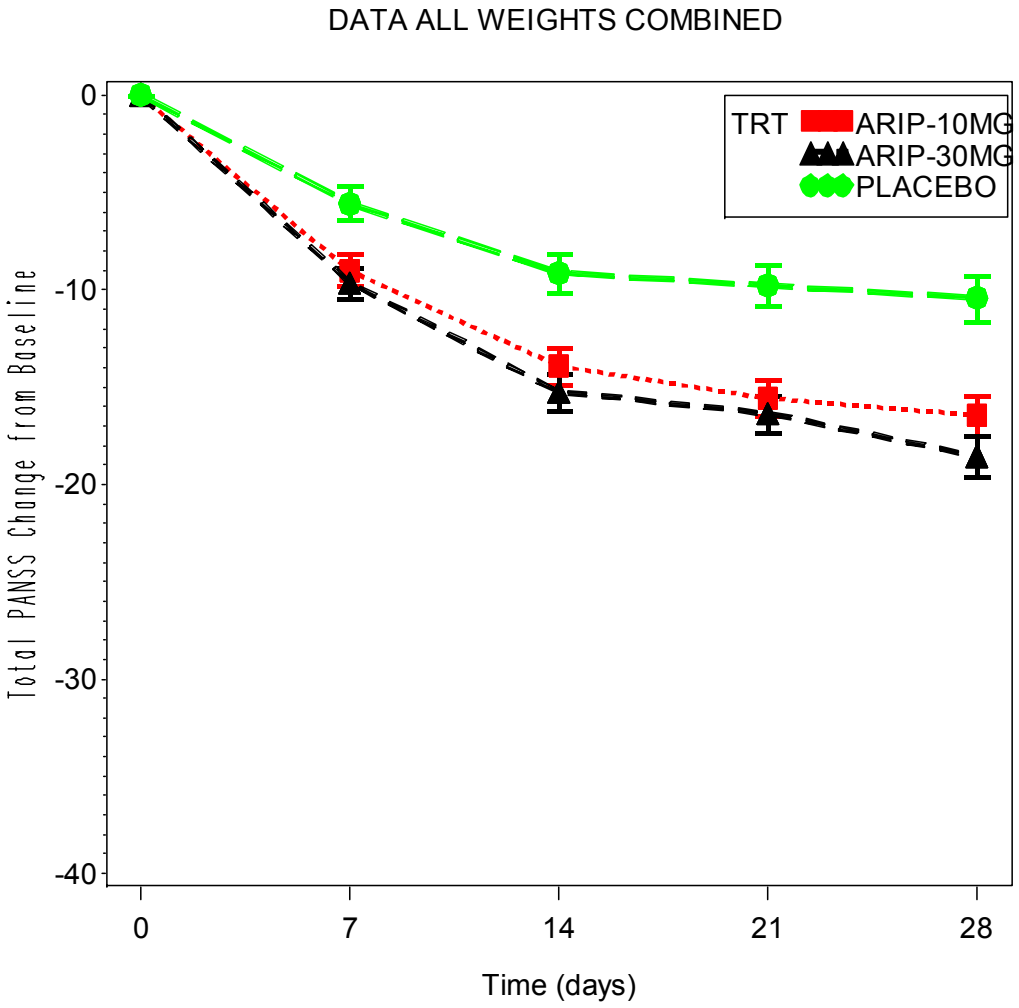


Figure 21. Analysis of YMRS scores as a function of time with all children data combined.

ADVERSE EFFECTS

Table 14. Most Severe Reported Treatment-emergent Adverse Events by 5% or Greater Incidence in Any Treatment Group During the Acute Phase

Adverse Event	Aripiprazole 10 mg (N = 98) n (%)	Aripiprazole 30 mg (N = 99) n (%)	Aripiprazole Placebo (N = 97) n (%)
Somnolence	19(19.4%)	26(26.3%)	3(3.1%)
Extrapyramidal Disorder	12(12.2%)	27(27.3%)	3(3.1%)

Somnolence

The percent of occurrence of the main adverse effects, somnolence and extrapyrimidal effects, appeared to be dose related for the children with bipolar disorder.

PHARMACOKINETIC COMMENTS

1.The model developed by the firm has a bias towards under predicting the upper tail (i.e., concentrations above 600 ng/ml) of the distribution (predictive check) (Figure 5) of the mean trough concentrations. It is apparent that the experimental values are underestimated for about 25-30% of the data between the 50th and 75th quantiles. The major impact would be to underestimate Cmax for study 238 (intensive sampling) and plasma levels in study 239. The underprediction would not have a major impact on study 240 since there were only 22 samples above 600 ng/ml (i.e., where the most underpredictions occurred).

2. The population PK of aripiprazole in children and adolescent patients ages 10-17 was described by a one-compartment allometrically scaled model with first-order absorption and elimination. The equations include a fixed power value of 0.75 for CL/F and 1.0 for V/F.

$$(Cl/F) = (Cl/F)_{TV} \cdot \left(\frac{LBW_i}{LBW_{ref}}\right)^{0.75}$$

$$(V/F) = (V/F)_{TV} \cdot \left(\frac{Wt_i}{Wt_{ref}} \right)^{1.0}$$

Use of 0.75 as a scaling factor for Cl and 1 for Volume in children was not supported by the covariate model fit. There was a change in objective function and in the intersubject variability for volume. However, the relationship between clearance and body weight was not greatly impacted as noted by the small change in intersubject variability with the weight covariate in the model.

4. Pediatric pharmacokinetics appear to be similar to adults based on an informal comparison with an historical adult population.

5. Pharmacokinetic parameters obtained from the FDA analysis using the same model (Appendix I) are in agreement with those submitted by the firm.

SCHIZOPHRENIA COMMENTS

6. The drop-out pattern indicated that a higher drop-out rate is related to a higher dose at day 35.

7. The occurrence of the main adverse effects, somnolence and extrapyrimidal effects, were dose related for the children in schizophrenia study 239.

BIPOLAR COMMENTS

8. Drop-outs by day and dose group were highest for the placebo and 30 mg dose groups.

9. Adverse effects for somnolence and extrapyrimidal effects were dose related.

FDA LABEL

A labeling review was done on the [redacted] submission. The current proposed label is consistent with that reviewed label. The contents of that

labeling review has been included in this review with an addition for treatment of bi-polar disorder in children.

PROPOSED PEDIATRIC PATIENTS

1.1Schizophrenia

ABILIFY is indicated for the acute treatment of schizophrenia in 13 to 17 years of age [see *CLINICAL STUDIES (14.1)*].

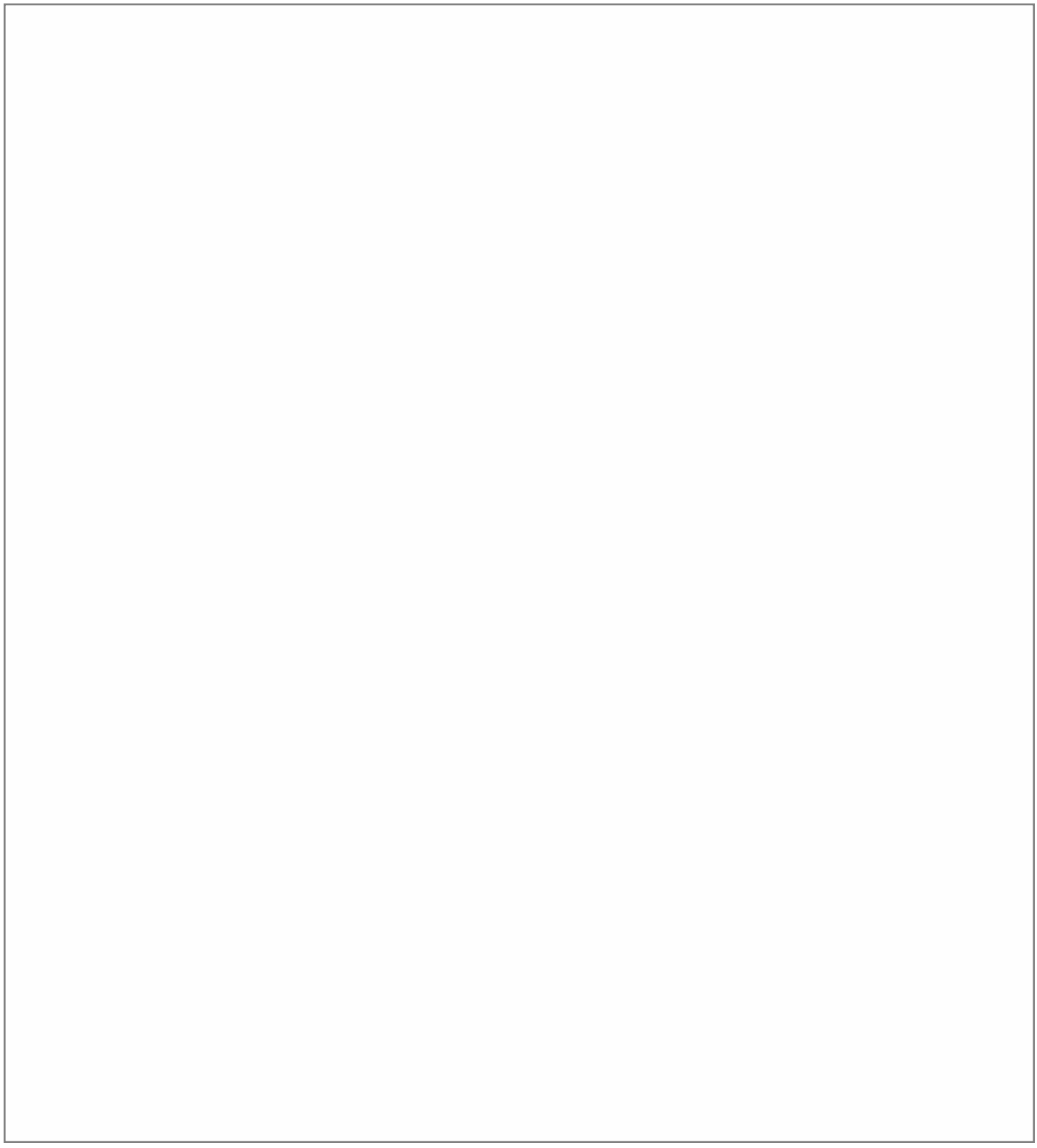
PROPOSED DOSAGE AND ADMINISTRATION

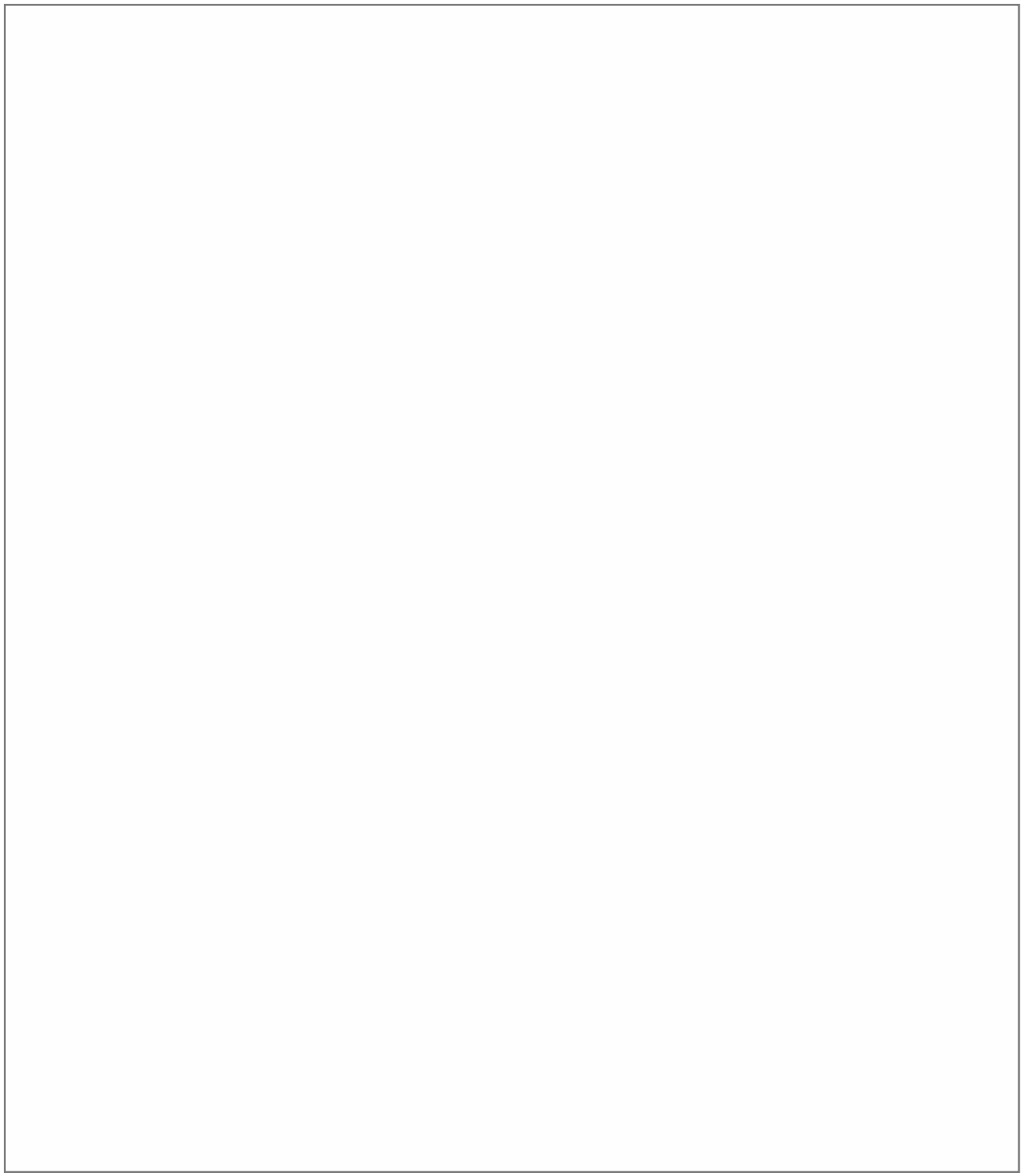
2.Dosage and Administration

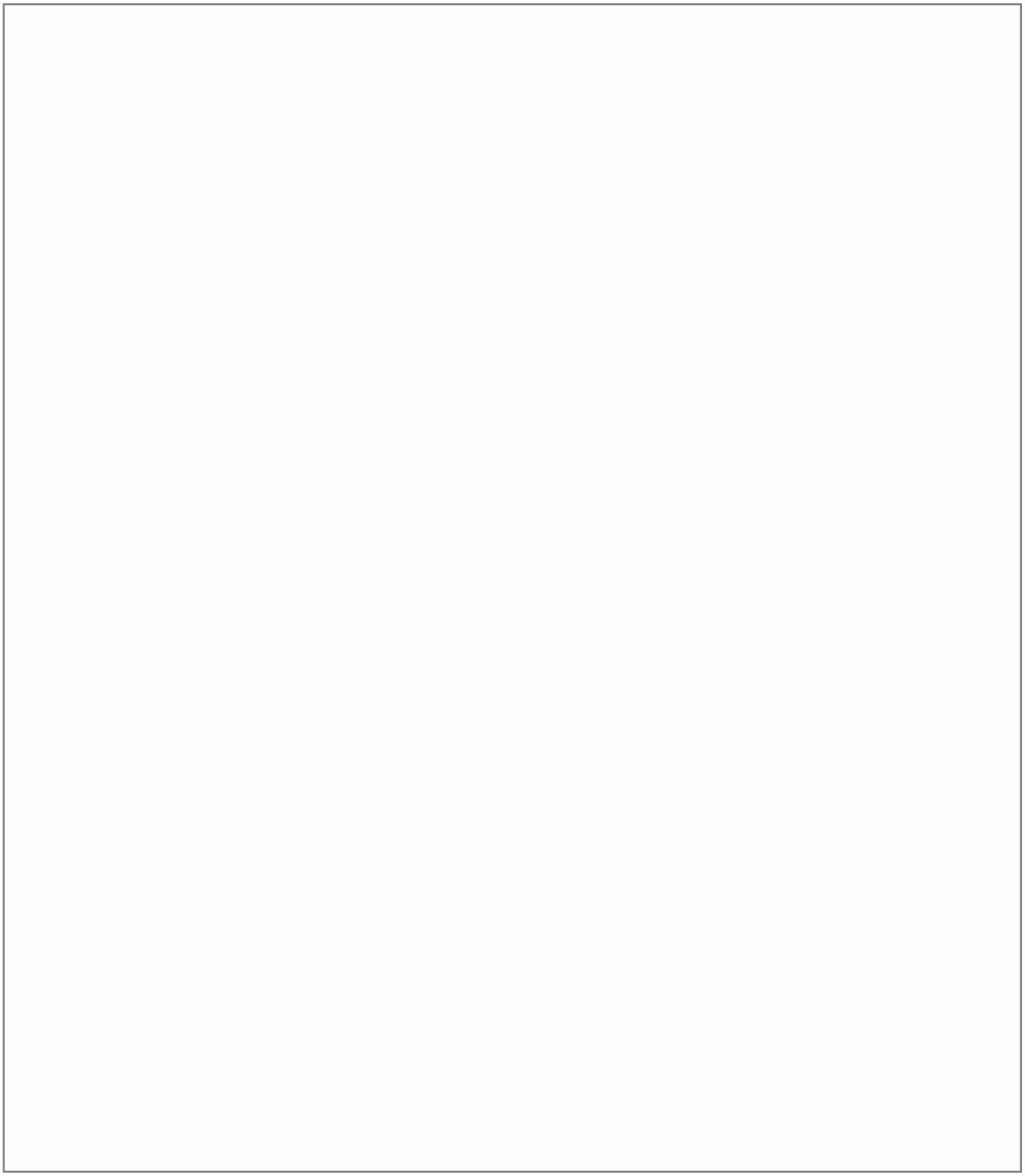
2.1 Schizophrenia

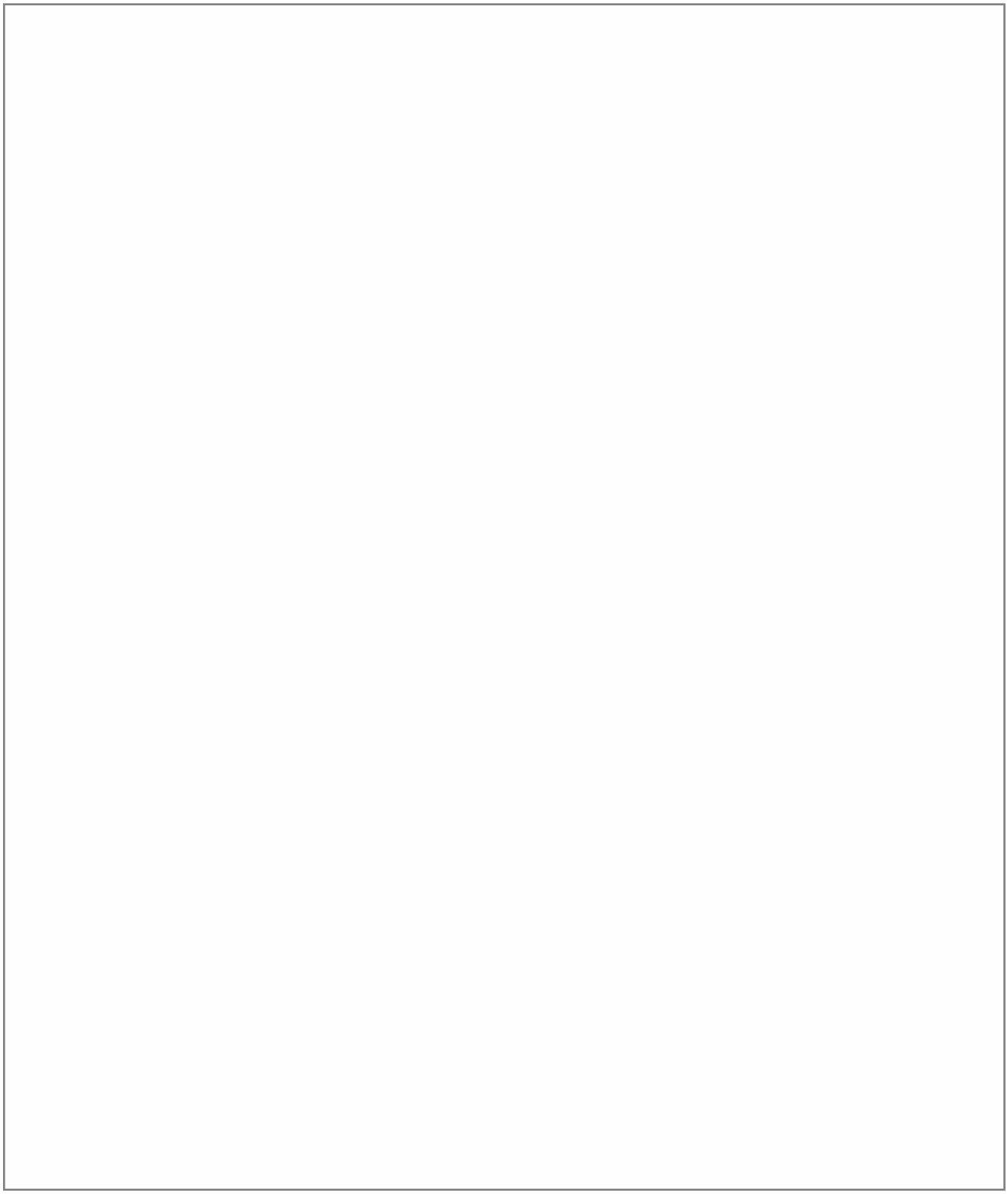
Usual Dose

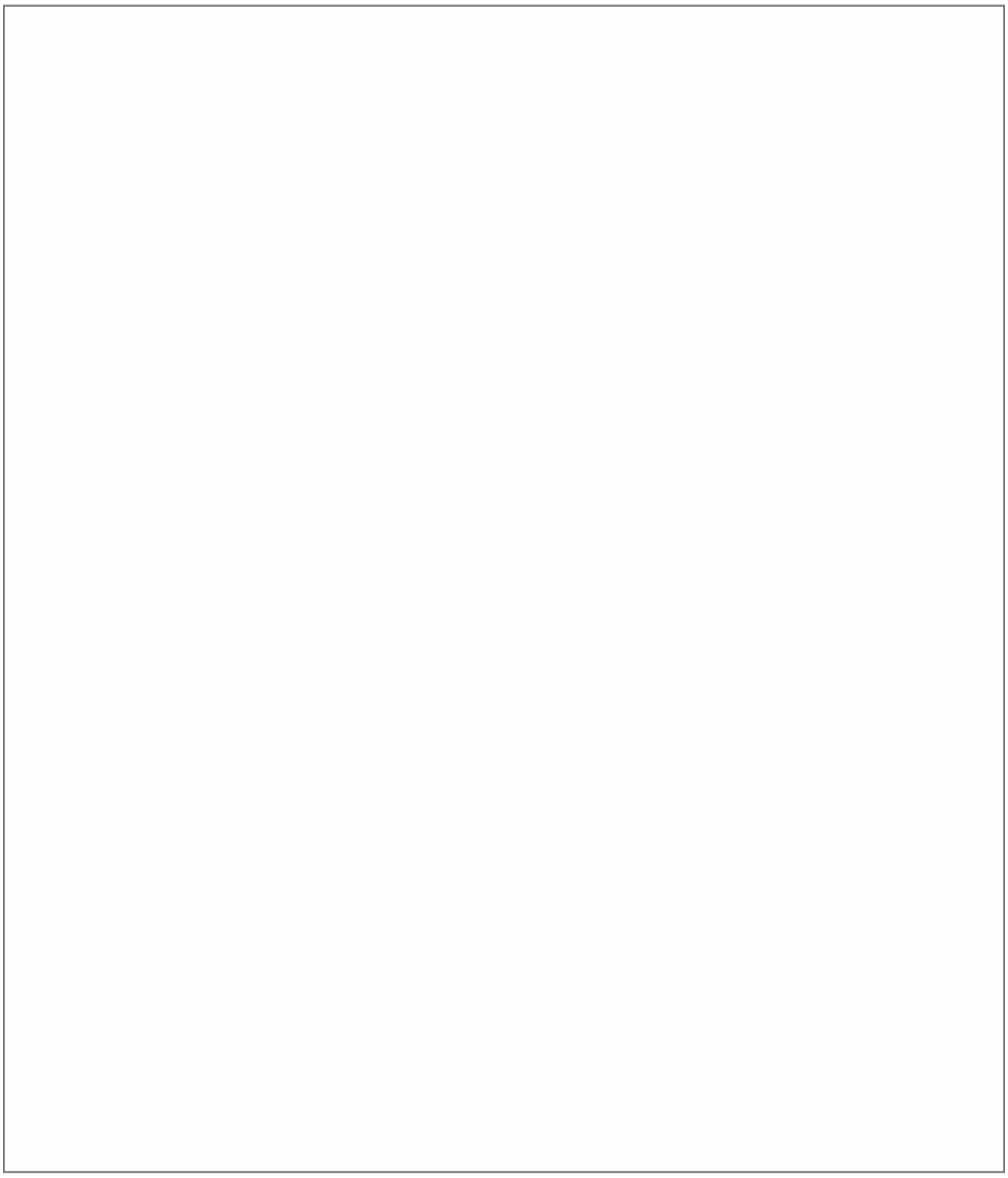
Pediatric Patients

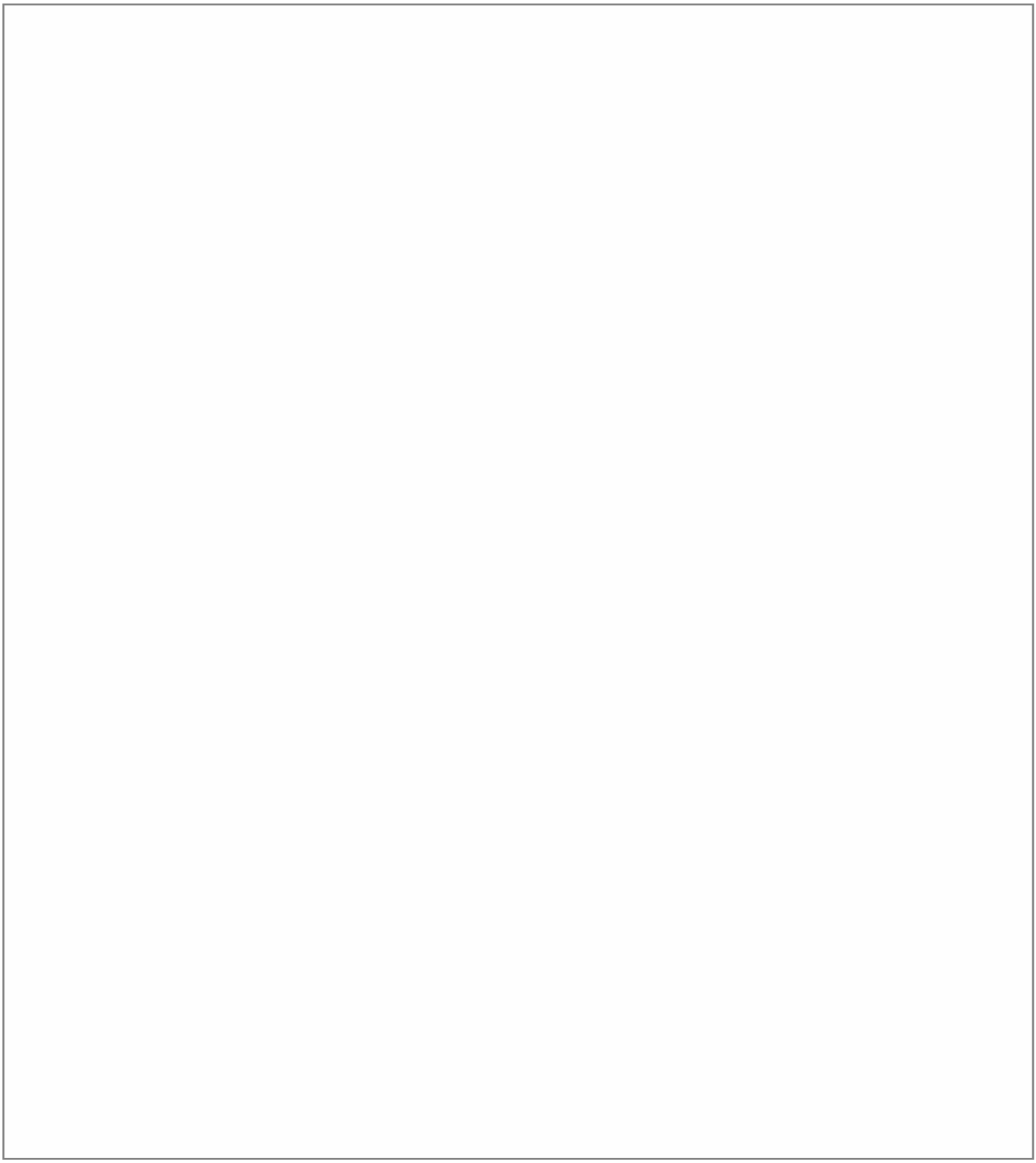


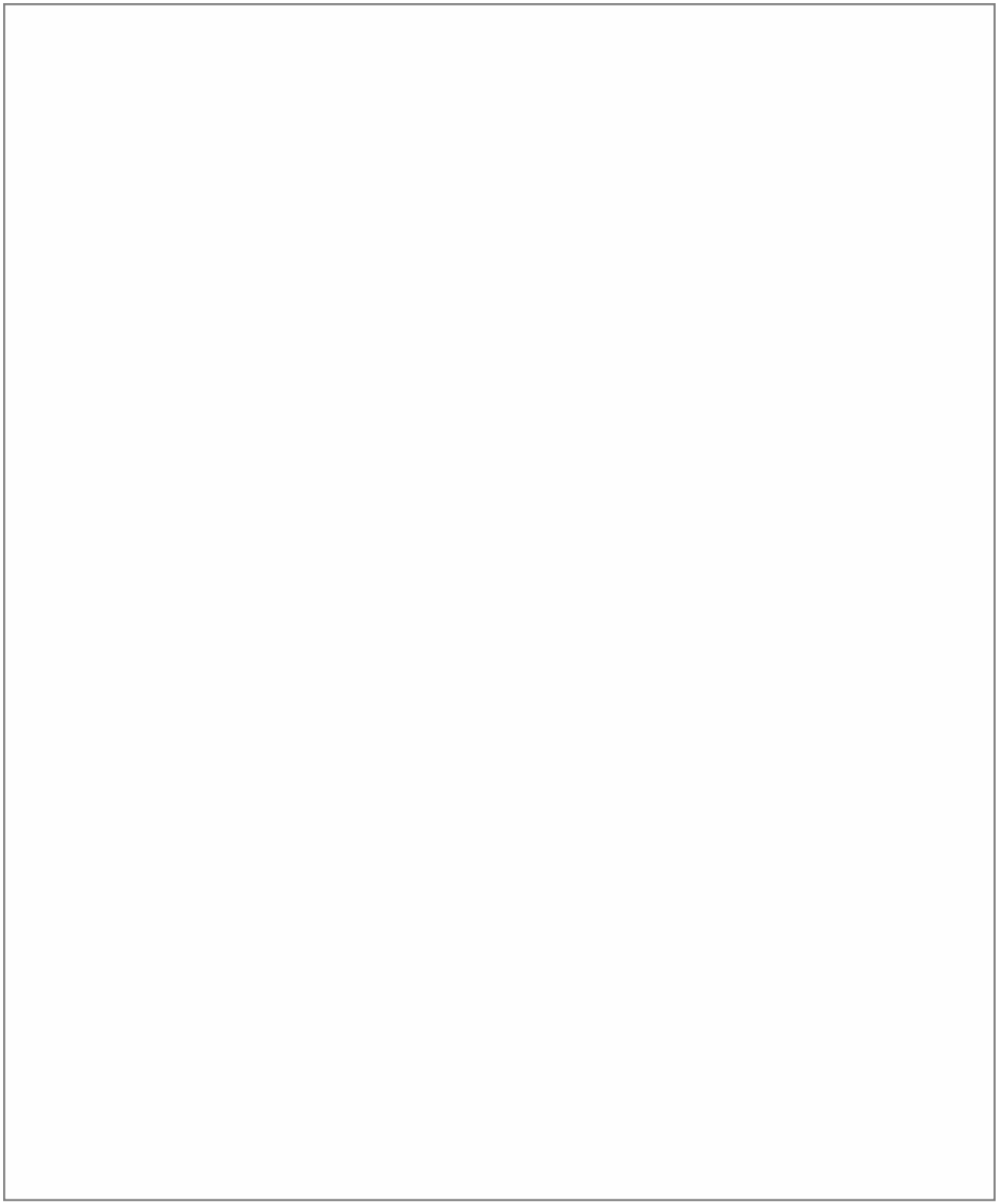


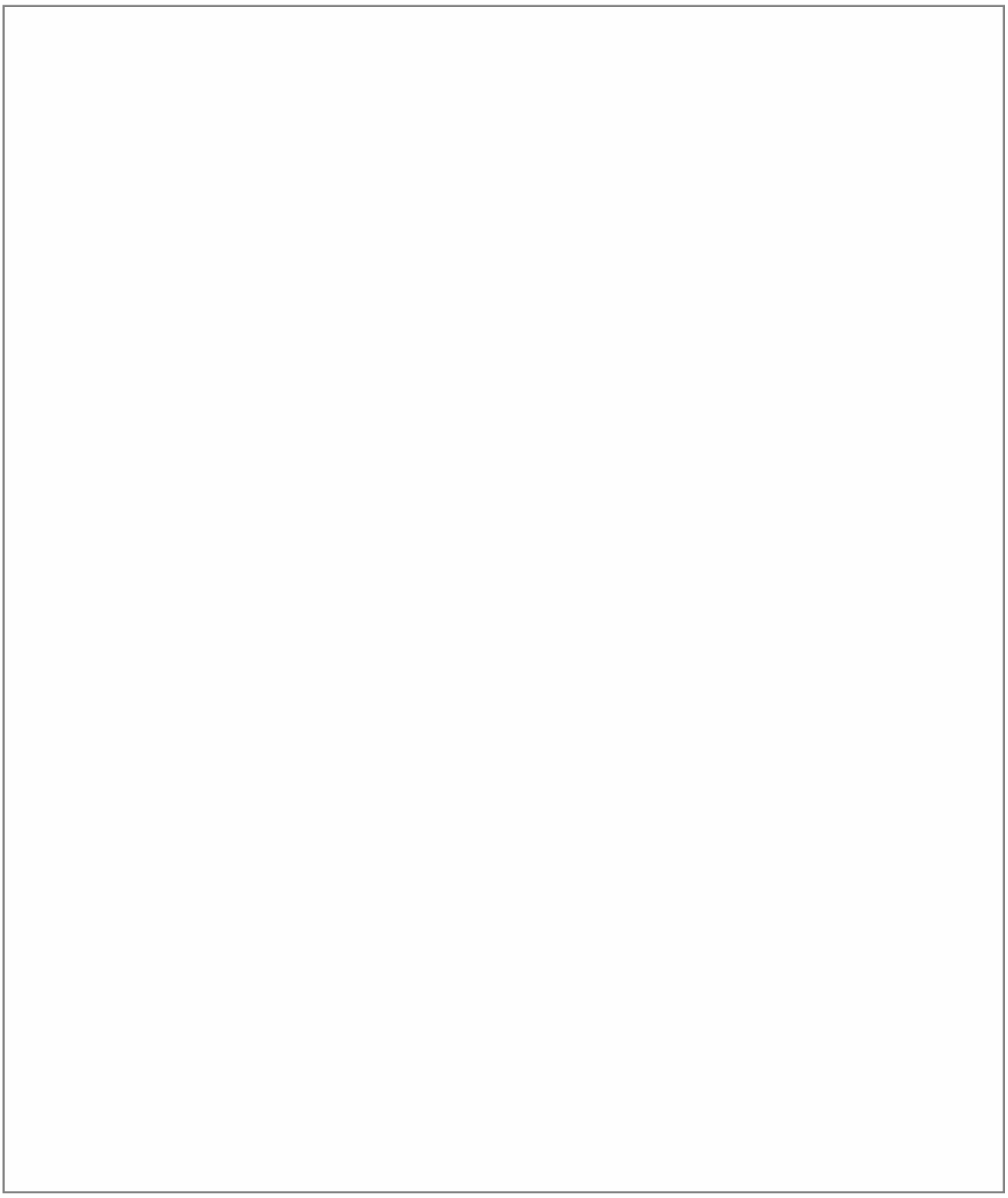


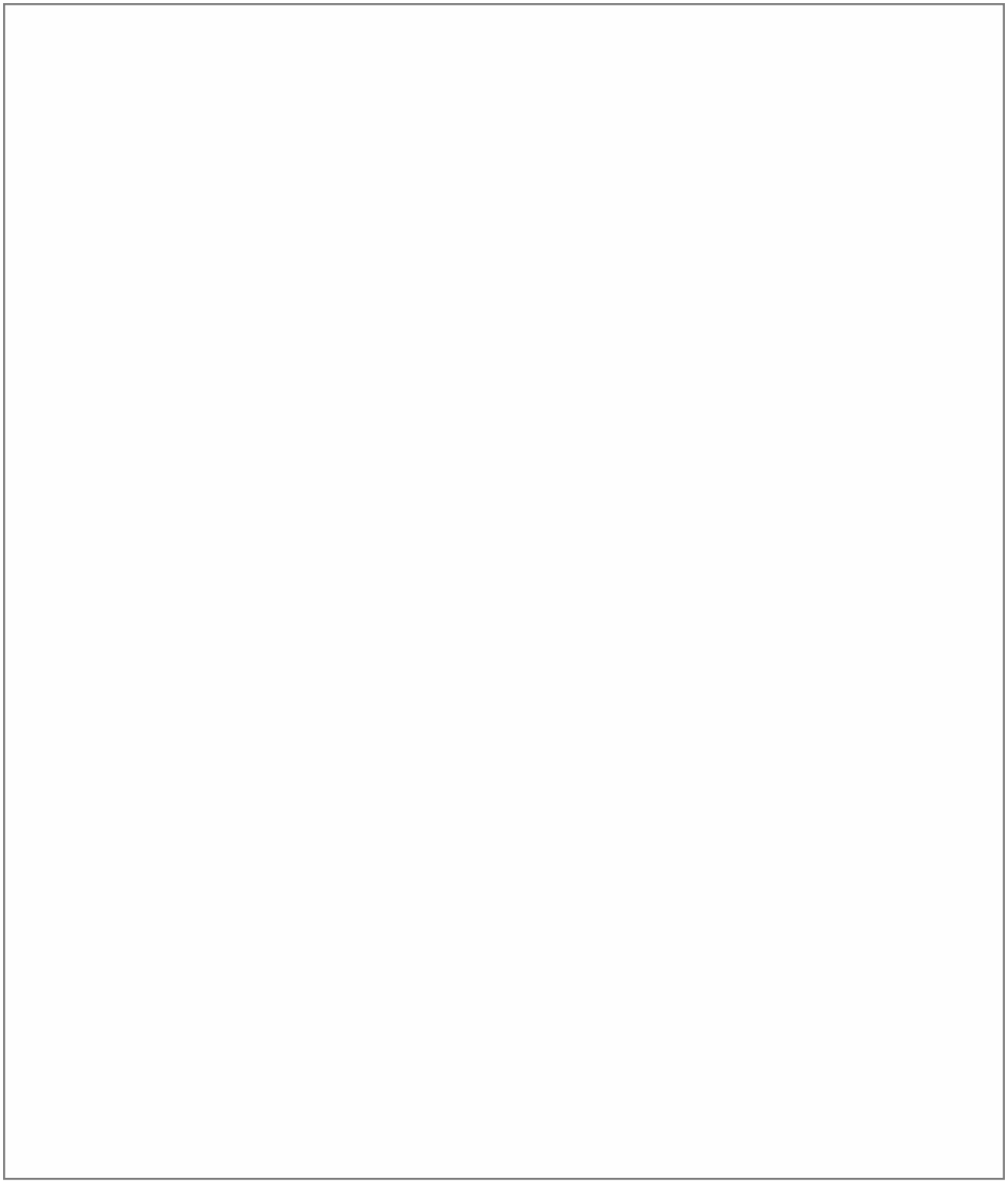












SIGNATURES

Andre Jackson_____
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Office of Clinical Pharmacology and Biopharmaceutics

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Team Leader, Psychiatry Drug Section, DCP I
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RD/FTinitialized by Joga Gobburu, Ph.D. for Yaning Wang, Ph.D./
_____
Team Leader Pharmacometrics

cc: NDA 21-436, HFD-860(Mehta, Baweja, Jackson,Wang, Gobburu)

APPENDIX I

FIRM'S ANALYSIS

The firm's data set nmv238239240, which contained the data from all 3 studies, was visually inspected based upon the data dictionary supplied by the firm and the data was consistent with the variable names and contained the proper type of variable(i.e., time evid etc).

PKT- 4 **Pediatric Final Model**

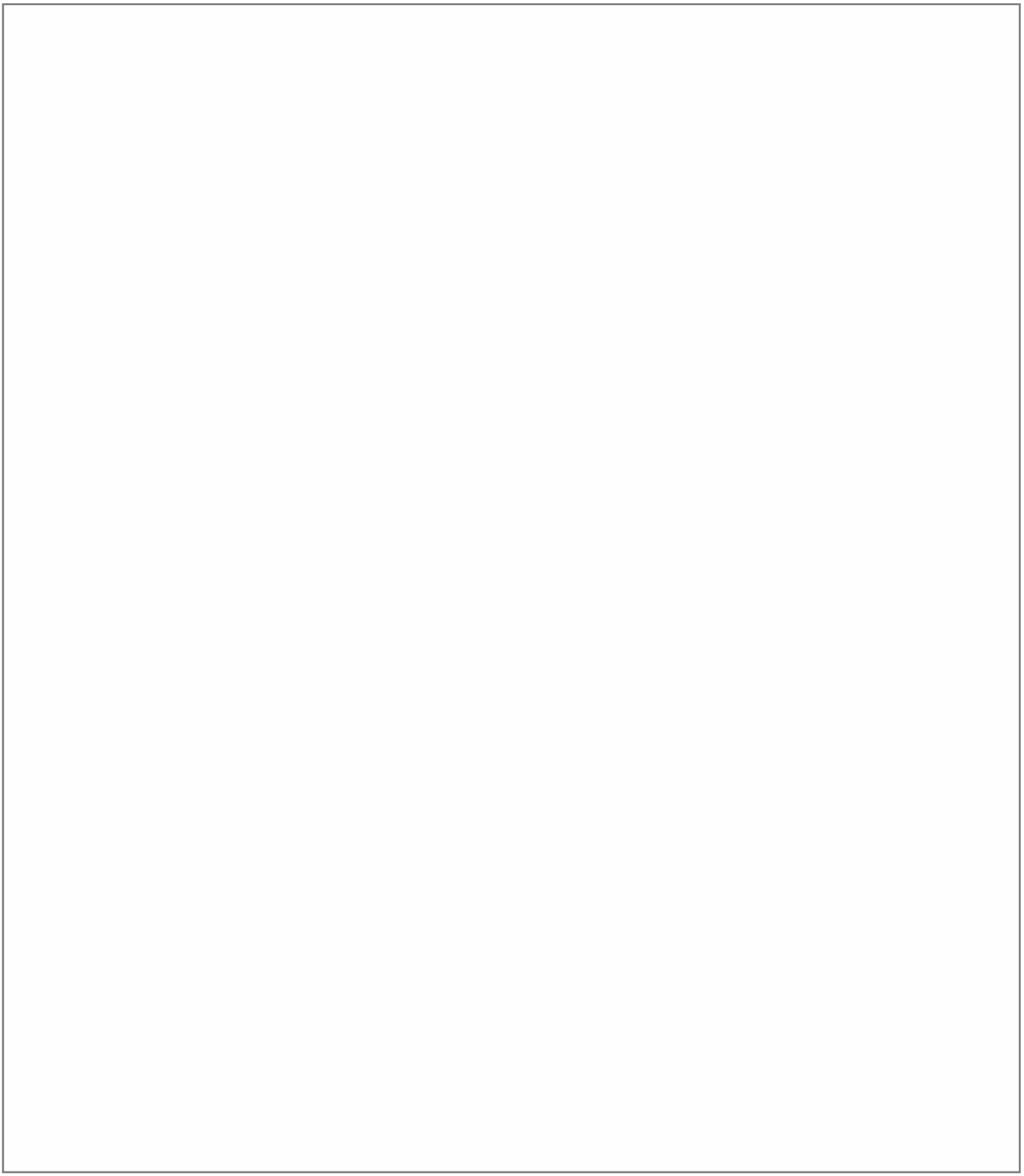
Parameter	Parameter estimate[b]	%RSE[a]	95% Confidence interval[b]		CV%
			Lower bound	Upper bound	
THETA					
CL/F	3.44	2.76%	3.26	3.63	
V/F	255	4.98%	231	283	
ka	1.67	25.5%	0.748	4.28	
OMEGA					
ω^2CL (1,1)	0.208	12.1%	0.164	0.260	45.6%
ω^2V,CL(2,1)	0.051	64.1%	-0.011	0.117*	
ω^2V(2,2)	0.199	34.9%	0.048	0.382	44.6%
ω^2Ka,CL(3,1)	-0.038	215%	-0.240	0.155*	
ω^2Ka,V(3,2)	0.315	35.1%	-0.070	0.691	
ω^2Ka(3,3)	2.57	36.9%	0.365	12	160%
SIGMA					
1,1	319	23.3%	177	494	17.8 (SD)
2,2	0.0481	16.3%	0.033	0.063	21.9%

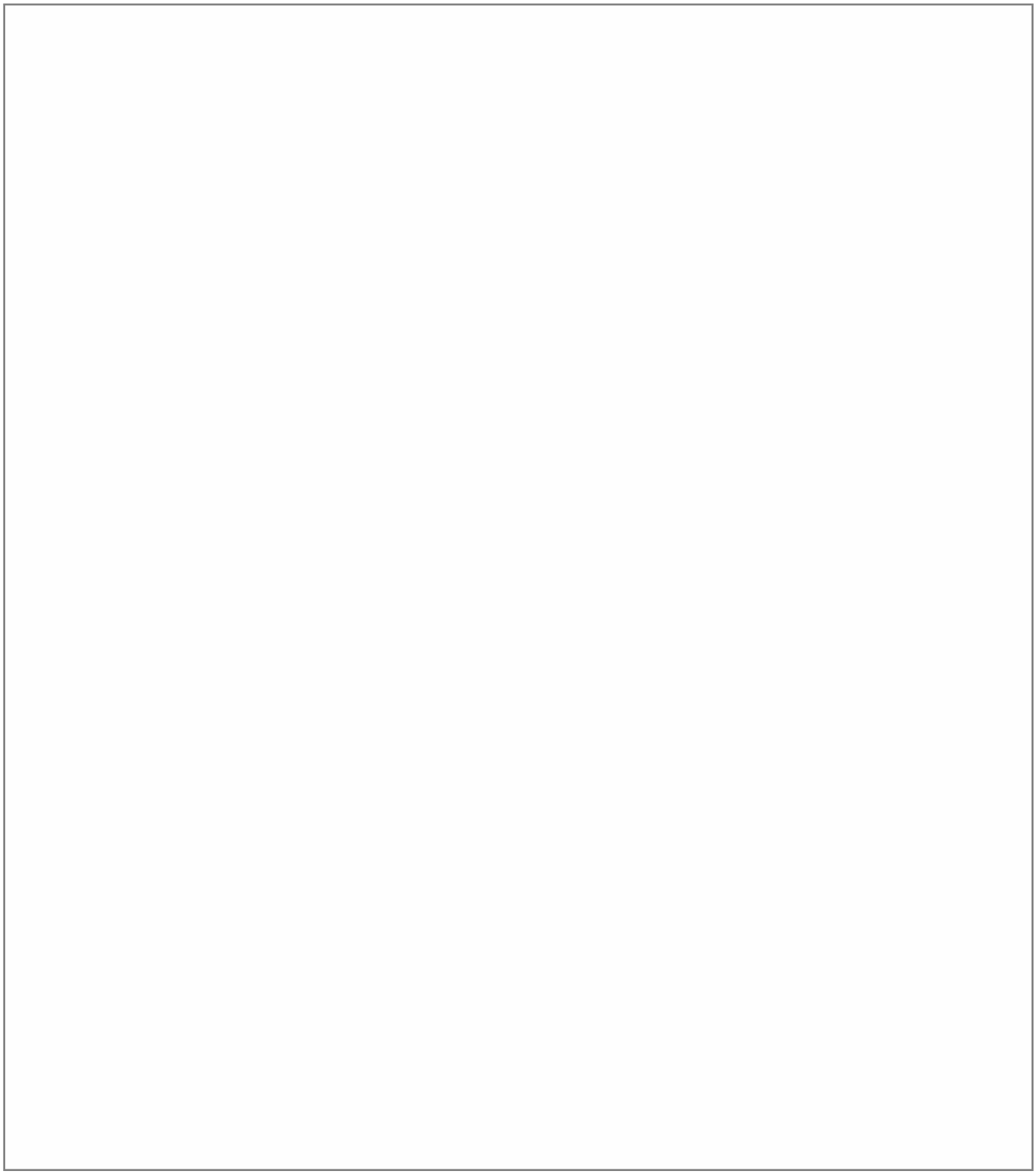
*Indicates 95% confidence interval that includes zero

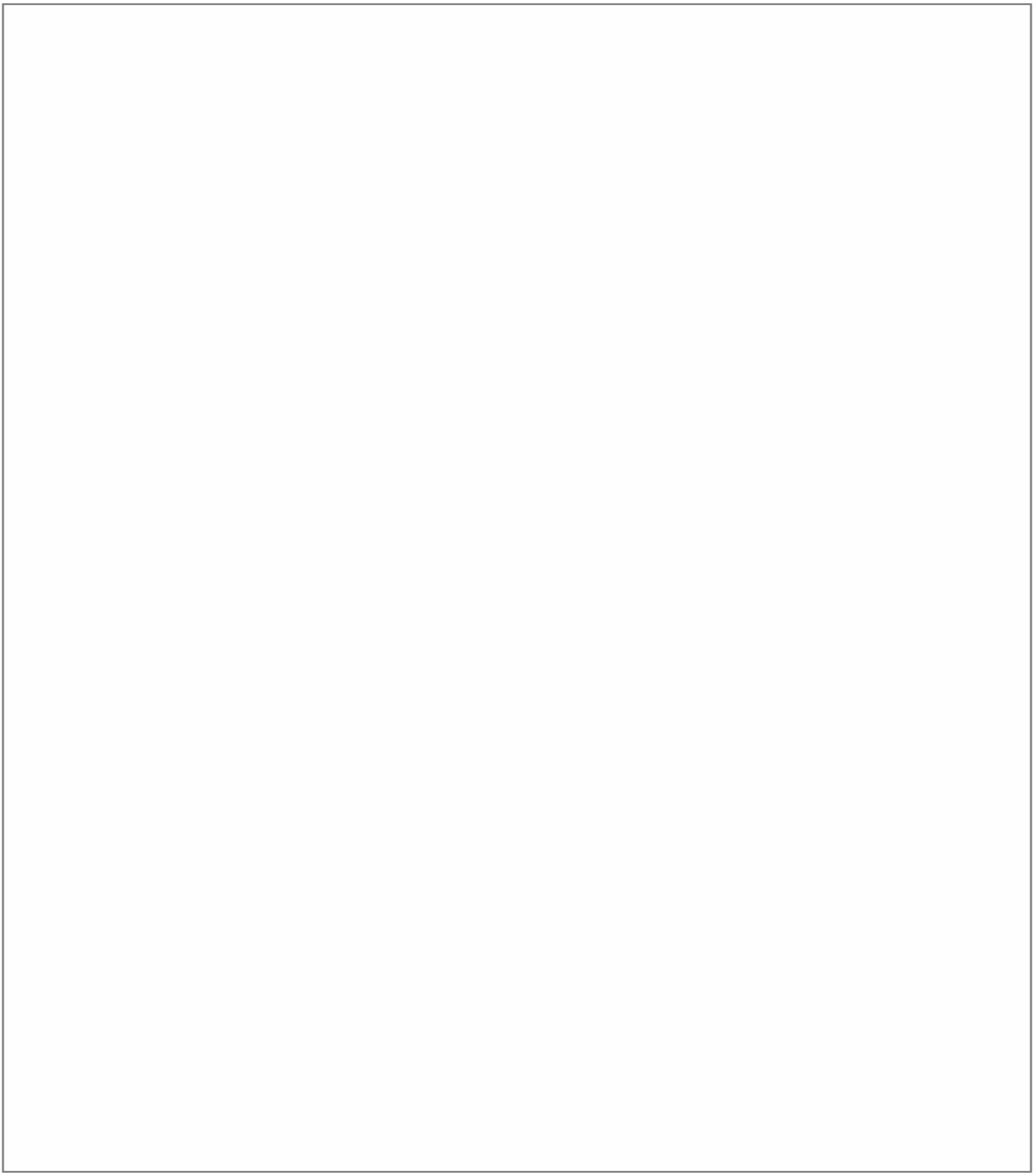
a %RSE is percent relative standard error (100% x SE/EST)

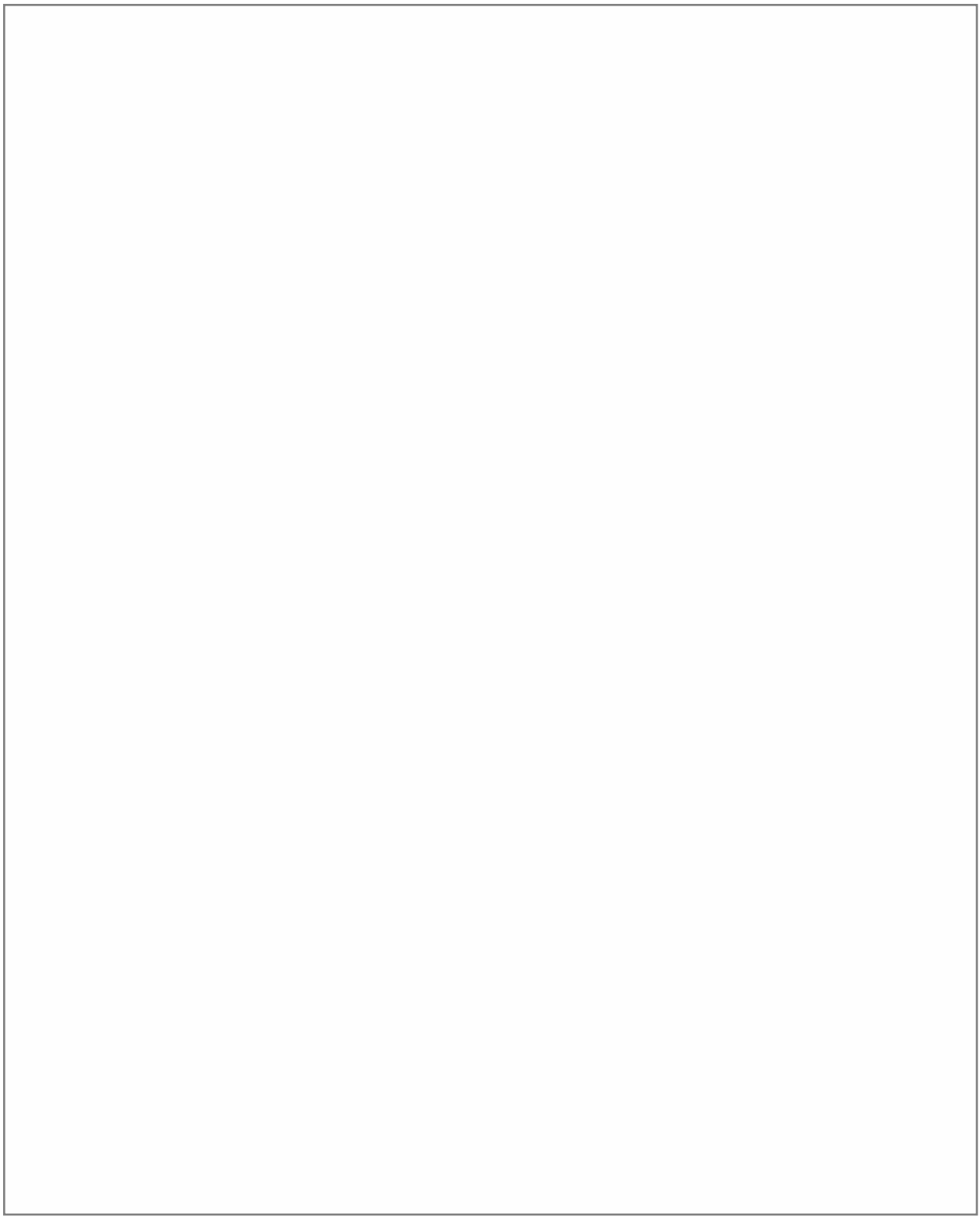
b Estimates based on Bootstrap (PKT-5)

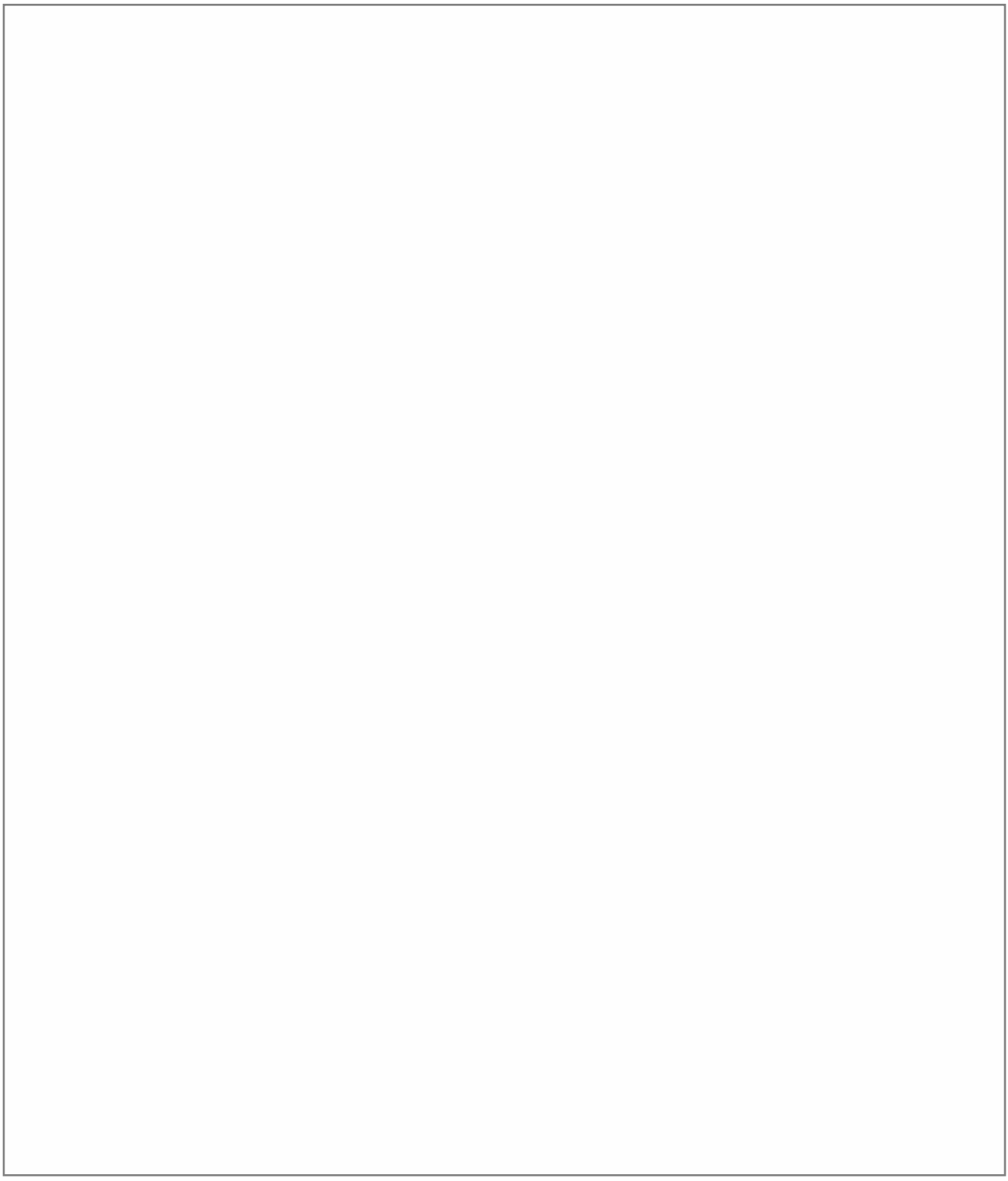
FDA ANALYSIS-Repeat of Firm's analysis











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/s/

Andre Jackson
2/19/2008 10:00:23 AM
BIOPHARMACEUTICS

Yaning Wang
2/19/2008 01:34:17 PM
BIOPHARMACEUTICS

Raman Baweja
2/20/2008 11:40:35 AM
BIOPHARMACEUTICS
DFS of NDA 21436/021; 21713/016; 21729/008; 21866/008 -- Bipolar Disorder in Pediatric Patients