CLINICAL REVIEW

Application Type	NDA 21436-021 NDA 21713-016 NDA 21729-008 NDA 21866-008
Submission Number	021
Submission Code	SE5
Letter Date	August 28, 2007
Stamp Date	August 29, 2007
PDUFA Goal Date	February 29, 2008
Reviewer Name	Jing Zhang, MD, PhD
Review Completion Date	February 14, 2008
Established Name	Aripiprazole
(Proposed) Trade Name	Abilify®
Therapeutic Class	Atypical Antipsychotics
Applicant	Otsuka Pharmaceutical Company
Priority Designation	P
Formulation	2, 5, 10 and 15 mg Oral Tablets
Dosing Regimen	10 mg and 30 mg
Indication	Bipolar Mania or Mixed Episodes
Intended Population	Children/Adolescents

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, I recommend that this supplement NDA be granted approvable status.

The sponsor proposed [redacted] acute [redacted] indications in the treatment of manic and mixed episodes with or without psychotic features associated with bipolar I disorder in pediatric population (10 to 17 yrs). The acute treatment indication was well supported by the efficacy data from the Acute Phase of Study 31-03-240. [redacted] Therefore, I recommend that only the acute treatment indication to be approved.

A few labeling changes were recommended. Details can be found in section 9.4 Labeling Review.

Final approval is contingent on mutual agreement on treatment indications and labeling changes.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no additional recommendations for risk management activity.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are recommended at this time.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In response to the FDA's Pediatric Written Request (PWR) dated February 11, 2003, the sponsor designed the aripiprazole pediatric efficacy program (APEX) to provide controlled clinical data regarding the use of aripiprazole for the treatment of schizophrenia in the adolescent population and mania associated with bipolar disorder in the child and adolescent population. The APEX

program included four studies: one safety, tolerability and pharmacokinetic (PK) study (31-03-238), two randomized, double-blind, placebo-controlled safety and efficacy study—one for schizophrenia (31-03-239) and one for bipolar mania (31-03-240), and a roll-over, open-label long-term safety study (31-03-241) for subjects who complete either of the double-blind trials.

Data from Study 31-03-238 (PK study), 31-03-239 (acute controlled study for adolescent schizophrenia) and 31-03-241(long-term, open label safety study with cut off date of 9 Nov. 2006) were submitted to NDA 21436/017, aripiprazole for the indication of pediatric schizophrenia. This sNDA has been approved by FDA on 29 Oct. 2007.

This submission includes data from Study 31-03-240 and 31-03-241. From this submission, the sponsor intended to seek for approval of the acute [redacted] treatment indications of manic and mixed episodes with or without psychotic features associated with bipolar I disorder in children and adolescents ages 10 to 17 years.

The primary components of this supplement NDA are as follows:

- Clinical study report (CSR) for study 31-03-240 (PWR required; placebo-controlled efficacy and safety study in the pediatric bipolar disorder population)
- CSR for study 31-03-241 (PWR required; open-label, long-term safety study in pediatric schizophrenia and bipolar disorder populations)
- CSR for 31-05-242 (APEX Program Population Pharmacokinetic (PK) Report of aripiprazole in pediatric schizophrenia and bipolar disorder populations from the 31-03-238, 31-03-239 and 31-03-240 studies)
- Combined Safety Summary Report
- Revised Abilify labeling for the pediatric bipolar disorder indication in Physician's Labeling Rule (PLR) format

1.3.2 Efficacy

The efficacy of aripiprazole in the acute treatment of manic and mixed episodes associated with bipolar I disorder in a pediatric (10 to 17 yrs) population was demonstrated by efficacy data from the Acute Phase of Study 31-03-240. Aripiprazole showed efficacy at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared to placebo in the primary efficacy variable, mean change in YMRS Total Score from baseline to Week 4 (LOCF).

1.3.3 Safety

The safety review was based on the safety data from Study 31-03-240 and 31-03-241. The safety findings from this submission were comparable to that obtained from adult bipolar clinical trials with the exception of some AEs (eg, somnolence, blurred vision, and extrapyramidal symptoms) appeared to occur at a higher frequency in the pediatric population. No any unexpected serious adverse events (SAEs) or deaths associated with aripiprazole treatment were reported.

1.3.4 Dosing Regimen and Administration

Study 31-03-240 was a fixed-dose study. Eligible patients were randomized into one of following treatment groups: aripiprazole 10 mg/d, aripiprazole 30 mg/d and placebo. All study medications were administered orally. Subjects reached their target dose through a forced titration schedule and proceeded with treatment at their target dose until the end of the Acute Phase (4 weeks).

1.3.5 Drug-Drug Interactions

The existing aripiprazole label addresses safety outcome related to potential drug-drug interactions. There have been no new data generated on this topic from this submission.

1.3.6 Special Populations

All two studies submitted to this sNDA are pediatric studies. There are no new data generated on other special populations from this submission.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Aripiprazole is a dopamine presynaptic D_2 auto-receptor partial agonist and belongs to atypical antipsychotic family. Same as other atypical antipsychotics, aripiprazole also acts as an antagonist at serotonin 5-HT_{1A} receptor.

Abilify® (aripiprazole, OPC-14597, BMS-337039) is approved in the United States for the treatment of adults with acute schizophrenia (as of November 2002), maintenance of stability in schizophrenia (as of August 2003), treatment of acute manic and mixed episodes associated bipolar disorder (as of September 2004), and for the maintenance of efficacy in bipolar I disorder (as of 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.

Aripiprazole is approved in the USA for the acute treatment of pediatric schizophrenia in Oct. 2007.

2.2 Currently Available Treatment for Indications

Lithium is approved by FDA for pediatric bipolar disorder (age 12 and up). Risperidone is the only antipsychotic that has been approved by FDA for the indication of pediatric bipolar mania (Aug. 2007). However, mood stabilizers and antipsychotics, especially atypical antipsychotics, have been widely used off-label in real clinical practice for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

Aripiprazole is an approved drug in the United States.

2.4 Important Issues With Pharmacologically Related Products

Aripiprazole is the only FDA approved atypical antipsychotic with dopamine D_2 receptor partial agonist property. As a member of atypical antipsychotics, aripiprazole labeling carries same class warnings and precautions as other atypical antipsychotics. No important issues with pharmacologically related products were identified from this submission.

2.5 Presubmission Regulatory Activity

Feb. 11, 2003 Pediatric Written Request (PWR) for pediatric studies in schizophrenia and bipolar mania was issued by FDA to Otsuka.

Nov. 13, 2003 Otsuka met with FDA to discuss Abilify Pediatric Exclusivity Program.

June 8, 2004 A telecon was held on June 8th 2004 to discuss clarifications and proposals from Otsuka regarding FDA's PWR for Abilify.

Aug. 6, 2004 New protocol for Study 31-03-241 (adolescent bipolar mania study) was submitted to FDA.

July 5, 2007 Pre-NDA meeting with FDA discussed results of pediatric bipolar trial done in response to PWR and discussed possible sNDA submission seeking an indication in pediatric population.

Aug. 28, 2007 Otsuka submitted this sNDA for Ability in the treatment of pediatric bipolar disorder.

2.6 Other Relevant Background Information

Aripiprazole has not been withdrawn from the market for any reason.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Aripiprazole is a FDA approved drug. No new CMC data were submitted to this sNDA. Environmental assessment was not deemed necessary at this time point.

3.2 Animal Pharmacology/Toxicology

There is no animal pharmacology/toxicology data provided in this submission. These studies were not deemed necessary.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The efficacy data to support the efficacy claim of this submission came from Study 31-03-240. The safety data to support the safety conclusions in pediatric bipolar population came from Study 31-03-240 and Study 31-03-241.

4.2 Tables of Clinical Studies

Table 1 summarizes studies included in the efficacy and safety review for this submission.

Table 1 Clinical Studies Included in Efficacy and Safety Review

Protocol No. Study Design	Study Objective	Duration	Dose, and Regimen
31-03-240 A multicenter, randomized, double-blind, placebo controlled and fixed-dose study in treatment of adolescents with primary diagnosis of bipolar I disorder.	To assess the short-term and long-term safety, and efficacy of oral aripiprazole at doses of 10 mg/d and 30 mg/d in adolescents (10 to 17 years).	4 wk (acute phase) 24 wk (extension phase)	Arip 10 mg po qd Arip 30 mg po qd Placebo po qd
31-03-241 A multicenter, open-label and flexible-dose study in patients who completed Study 31-03-239 or had withdrawn from the double-blind extension phase of Study 31-03-240.	To assess the long-term safety and tolerability of flexible-dose aripiprazole in adolescent patients with diagnosis of schizophrenia.	6 months	2 to 30 mg po qd

4.3 Review Strategy

A list of the items examined during the course of this review is provided in Table 2.

Table 2 Items Utilized in the Review

Submission Date	Submission Type	Items Reviewed
Aug. 28, 2007	Initial sNDA	CSR for Study 31-03-240 CSR for study 31-03-241 Combined Safety Summary Report Revised Abilify labeling for the pediatric bipolar disorder indication Case report tabulations (.xpt files) Case report forms
Sept. 27, 2007	Amendment	Updated literature search
Nov. 8, 2007	Amendment	Safety Update

4.4 Data Quality and Integrity

An audit of the Case Report Forms (CRFs), Narrative Summaries and adverse event data listing was conducted for two patients (03240-21-5275 and 03240-913-5119, ~5% of the 49 patients with submitted CRFs), whom I randomly selected from the database from Study 31-03-240. The AE data listings examined were AE0.xpt from Study 31-03-240 datasets. The consistency of AE data across CRFs, Narrative Summaries and AE0.xpt file was examined. An examination of the AE information across these sources for this subject revealed reasonable consistency and completeness.

4.5 Compliance with Good Clinical Practices

All studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

4.6 Financial Disclosures

Dr. [redacted] received payments from [redacted] for lectures given under strict PHARMA guidelines and participated in speaker training sessions. The cumulative value of the payments received between [redacted] through [redacted] was in excess of $25,000.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Andre J. Jackson, PhD., is the clinical pharmacology reviewer for this submission. Please refer to Dr. Jackson's review for pertinent information.

5.2 Pharmacodynamics

Andre J. Jackson, PhD., is the clinical pharmacology reviewer for this submission. Please refer to Dr. Jackson's review for pertinent information.

5.3 Exposure-Response Relationships

Exposure-response relationship was not particularly studied in these studies. In the Acute Phase of Study 31-03-240, aripiprazole 30 mg arm was numerically superior to aripiprazole 10 mg arm in mean change from baseline in Y-MRS Total Score (arip 10 mg vs 30 mg: -5.99 vs. -8.26).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor intends to claim [ ] acute [ ] indications for child/adolescent bipolar I disorder, manic or mixed episodes with or without psychotic features.

6.1.1 Methods

Study 31-03-240 is the only placebo-controlled study that the sponsor submitted to support their efficacy claim in bipolar disorder, manic and mixed episodes. Study 31-03-240 consists of a 4-week acute treatment phase and a 24-week extension phase. The study design of the acute treatment phase meets PWR's requirements and is considered by the agency as a valid acute treatment study. The efficacy results from the acute treatment phase were reviewed in detail in this review.

[ ]

6.1.2 General Discussion of Endpoint

The primary endpoint for the Study 31-03-240 was the change from baseline to Week 4 (Acute phase) on the Young Mania Rating Scale (YMRS) total score. The YMRS is one of the most frequently utilized rating scales to assess manic symptoms in both adult and pediatric patients. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. Additional information is based upon clinical observations made during the course of the clinical interview. Strengths of the YMRS include its brevity, widely accepted use, and ease of administration in pediatric as well as adult populations.

6.1.3 Study Design

6.1.3.1 Investigators/Sites

Study 31-03-240 was conducted in 59 centers in the United States from 30 March 2005 to 16 February 2007. A full list of the principle investigators and clinical study sites were listed in Appendices 10.1.

6.1.3.2 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.

6.1.3.3 Subjects

Key Inclusion Criteria:

- Male and female aged 10 to 17, with a Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) confirmed DSM-IV diagnosis of bipolar I disorder, manic or mixed episode, with or without psychotic features. Co-morbid diagnoses were permitted including Attention Deficit/Hyperactivity Disorder (ADHD), Conduct Disorder (CD), and Oppositional Defiant Disorder (ODD) and anxiety disorders (except Post Traumatic Stress Disorder [PTSD] and Obsessive Compulsive Disorder [OCD]).
- YMRS score $\geq$ 20 at baseline

Key Exclusion Criteria:

- Subjects who presented with a clinical picture and/or history that was consistent with an Axis I (DSM-IV) diagnosis of Bipolar II Disorder, Bipolar Disorder Not Otherwise

Specified (NOS), Autism, Pervasive Developmental Disorder (PDD), OCD, PTSD, Mental Retardation or Schizophrenia or Schizoaffective Disorder.

- Subjects who have psychotic symptoms that were better accounted for by another general medical condition or direct psychological effect of a substance (ie, medications).
- Subjects who were considered treatment resistant to neuroleptics, in the opinion of the investigator, based on prior trials of two different neuroleptics that were of adequate dose and duration.
- Subjects with a history of neuroleptic malignant syndrome
- Subjects who presented a significant suicidal risk, or with a Suicidal Ideation Item of the Child Depression Rating Scale-Revised (CDRS-R) > 3.
- Subjects who have serious or unstable medical condition.
- Subjects who had been previously involved in a clinical study with aripiprazole or were currently treated with aripiprazole.
- Subjects who had participated in any clinical trial with an investigational product within the past month.

6.1.3.4 Overall Study Design

This study was a out/in-patient, multi-center, randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in child and adolescent subjects, ages 10 to 17 years, with a diagnosis of bipolar I disorder, manic or mixed episode, with or without psychotic features.

The study included two phases: a 4-week acute treatment phase and a 24-week extension phase. Patients who met inclusion criteria were randomized into one of 3 treatment arms: aripiprazole 10 mg, aripiprazole 30 mg or placebo arm, with a 1:1:1 ratio. Patients who completed 4-week acute treatment phase continued into the extension phase beginning at the same dose taken at the end of the acute phase.

Any mood-stabilizing medications, psychotropics, antidepressants and stimulants or other ADHD medications were discontinued for at least 5 half-lives prior to administration of study drug. During the course of study, patients could receive benzodiazepine or anticholinergics for clinical indications other than prophylactic use. Treatment with benzodiazepines within 4 hours prior to rating scale administration, or treatment with anticholinergic agents within 12 hours prior to rating scale administration, was prohibited.

Mandatory subject evaluations were to take place at Day 1 (Baseline), Day 4 (through phone call), and at Weeks 1, 2, 3, and 4 during the Acute Phase. Per the FDA's PWR, in the event of discontinuation, the study allowed for early rescue.

Subjects who completed the Acute Phase and took at least one dose of study medication in the Extension Phase were permitted to rollover into the open-label safety study, Protocol 31-03-241, to receive a cumulative total of up to 6 months of treatment with study medication.

6.1.3.5 Dose and Administration

This study was a fixed-dose study. Aripiprazole was gradually titrated to 10 mg within 5 days and to 30 mg within 13 days. Patients remained on their target dose for the remainder of the acute treatment phase. All study medications were administered orally.

6.1.3.6 Statistical Analysis Plan

A nominal overall significance level of 0.05 (two-tailed) was used in testing the statistical significance of the comparisons between aripiprazole 10 mg versus placebo and aripiprazole 30 mg versus placebo treatment groups. For the primary treatment comparisons of a dose group versus placebo, adjustment in testing due to multiple comparisons was handled by an overall F-test. Descriptive statistics for the Y-MRS total scores and change from baseline scores were presented by treatment group for Week 1 through Week 4 for both observed case (OC) and last observation carried forward (LOCF) datasets. The change scores were analyzed by using an analysis of covariance (ANCOVA) model with treatment as a factor, and baseline Y-MRS total score as a covariate. For comparing Y-MRS total scores between treatment groups at baseline, only treatment was included in the analysis of variance (ANOVA) model with baseline value as the dependent variable. Two-tailed student's t-tests were used to test differences between the LS means within the ANCOVA or ANOVA model.

6.1.4 Efficacy Findings

6.1.4.1 Disposition of Patients

The disposition of patients in the Acute Phase is summarized in Table 3. A total of 413 subjects were screened, and 296 subjects were randomized in this study: 98/296 (33.1%) in the aripiprazole 10 mg arm, 99/296 (33.4%) in the aripiprazole 30 mg arm, and 99/296 (33.4%) in the placebo arm. All randomized subjects were included in the efficacy analyses (randomized subjects evaluated for at least one primary or secondary efficacy parameter). A total of 294 subjects (99.3%) were treated and included in the safety analyses; 2 subjects from the placebo arm (2/99; 2%) were excluded from the safety analyses because they did not receive at least one dose of study drug.

Table 3 Disposition of Patients in Acute Phase of Study 31-03-240

Subjects	Acute Phase			
	Aripiprazole 10 mg (N = 98)	Aripiprazole 30 mg (N = 99)	Placebo (N = 99)	Total (N=296)
Screened	--	--	--	--
Randomized	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)
Adverse Experience	4 (4.1)	7 (7.1)	1 (1.0)	12 (4.1)
Lost to follow up	3 (3.1)	3 (3.0)	5 (5.1)	11 (3.7)
Subject met withdrawal criteria	--	--	--	--
Investigator withdrew subject	1 (1.0)	0 (0.0)	2 (2.0)	3 (1.0)
Subject withdrew consent	4 (4.1)	9 (9.1)	6 (6.1)	19 (6.4)
Protocol deviation	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.7)
Lack of efficacy as determined by investigator	2 (2.0)	2 (2.0)	8 (8.1)	12 (4.1)
Efficacy ITT[a]	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)
Safety ITT[c]	98 (100.0)	99 (100.0)	97 (98.0)	294 (99.3)

A high overall rate of retention (237/296 [80.1%]) was observed for the Acute Phase. Aripiprazole 10 mg arm had the highest completion rate (85.7%, 77.8%, and 76.8% in arip 10 mg, 30 mg and PLA respectively). Aripiprazole 30 mg arm was associated with higher rate of withdrawals due to AEs (7.1%) compared to aripiprazole 10 mg (4.1%) and placebo (1%). The placebo arm was associated with higher rate of withdrawals due to lack of efficacy.

6.1.4.2 Demographic Characteristics

Demographic characteristics are summarized in Table 4. The three treatment arms were demographically similar. The majority of subjects were male (159/296, 53.72%) and Caucasian (193/296, 65.20%). The mean age was 13.43 years (range, 10.0 to 17.0 years).

Table 4 Demographic Characteristics - All Randomized Subjects

Characteristic	Statistic	Arip 10 mg N = 98	Arip 30 mg N = 99	PLA N = 99	Total N = 296
Age (years)	Mean (SD)	13.70 (2.17)	13.31 (2.32)	13.28 (2.12)	13.43 (2.21)
Gender	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	Caucasian, n(%)	65 (66.33)	68 (68.69)	60 (60.61)	193 (65.20)
	Black, n(%)	24 (24.49)	8 (18.18)	23 (23.23)	65 (21.96)
	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	Arip 10 mg N = 98	Arip 30 mg N = 99	PLA N = 99	Total N = 296
Height (cm)	Mean (SD)	161.05(12.45)	158.37(12.21)	158.69(11.63)	159.36(12.12)
BMI	Mean (SD)	24.15 (5.37)	23.66 (6.70)	23.68 (4.98)	23.83 (5.72)

6.1.4.3 Disease Characteristics

Baseline disease severity, as measured by Y-MRS Total Score, Child Depression Rating Scale-Revised (CDRS-R) Suicidal Ideations Score, and treatment status for previous episodes, is presented in Table 5. Overall, the baseline disease severity was comparable across all treatment arms. The mean Y-MRS Total Score and CDRS-R Suicidal Ideations Score were 30.0 and 1.2, respectively. Mean baseline YMRS Total Scores by treatment group were 29.8, 29.5, and 30.7 in the aripiprazole 10 mg and 30 mg arms and the placebo arm, respectively. A total of 170/296 (57.40%) subjects had received treatment for previous episodes.

Table 5 Baseline Disease Characteristics

Baseline Characteristic	Statistic	Aripiprazole 10 mg (N = 98)	Aripiprazole 30 mg (N = 99)	Placebo (N = 99)	Total (N = 296)
Y-MRS Total Score	N Mean (SD) Range	98 29.8 (6.5) 20 - 45	99 29.5 (6.3) 20 - 46	99 30.7 (6.8) 16 - 50	296 30.0 (6.5) 16 - 50
CDRS-R Suicidal Ideation Score	N Mean (SD) Range	98 1.1 (0.4) 1 - 3	99 1.1 (0.5) 1 - 3	98 1.2 (0.5) 1 - 3	295 1.2 (0.5) 1 - 3
Treatment given for previous episodes	Yes, n (%) No, n (%)	57 (58.20) 41 (41.80)	50 (50.50) 49 (49.50)	63 (63.60) 36 (36.40)	170 (57.40) 126 (42.60)

6.1.4.4 Concomitant Medications

Concomitant use of benzodiazepines and anticolinergic medications was permitted under the investigator's instruction. During the acute treatment phase, the utilization rate of benzodiazepines was low and was similar across all treatment arms (7.1% in arip 10 mg, 8.1% in arip 30 mg, and 11.1% in PLA). Two patients in placebo arm were reported taking methylphenidate.

6.1.4.5 Efficacy Results

Primary Variable: YMRS Total Score change from baseline to endpoint

The mean change from baseline in YMRS Total Score by week is presented in Table 6 for the LOCF and the OC data set. Aripiprazole 10 mg and 30 mg showed statistically significant improvements over placebo in the YMRS Total Score at Week 4. Using the LOCF data set, the mean changes from baseline in YMRS Total Scores at Week 4 were −14.2 in the aripiprazole 10 mg arm, −16.5 in the aripiprazole 30 mg arm, and −8.2 in the placebo arm. The comparison

between aripiprazole and placebo was significant for both doses ($p < 0.0001$). The treatment effect was −5.99 (95% CI = −8.49 to −3.50) for the arip10 mg arm and −8.26 (95% CI = −10.7 to −5.77) for the arip 30 mg arm. Statistically significant improvements in YMRS Total Score were seen beginning at Week 1 for both aripiprazole doses and continued through Week 4.

OC analyses on the mean changes from baseline in YMRS Total Score at week 4 also demonstrated that both aripiprazole treatment arms were superior to placebo ($p < 0.0001$). The treatment effect was -5.81 for the apri 10 mg arm and -7.92 for the arip 30 mg arm. Statistically significant improvements in YMRS Total Score were seen beginning at Week 1 for both aripiprazole doses and continued through Week 4.

Table 6 Mean Change from Baseline in YMRS Total Score by Week in Acute Phase (LOCF & OC)

Visit/Week	Aripiprazole 10 mg N	Aripiprazole 10 mg LS Mean[a]	Aripiprazole 30 mg N	Aripiprazole 30 mg LS Mean[a]	Placebo N	Placebo LS Mean[a]	P-value[b] Aripiprazole 10 mg vs placebo	P-value[b] Aripiprazole 30 mg vs placebo
Baseline[c]	96	29.8	99	29.5	94	31.1	0.1702	0.0916
LOCF								
Week 1	92	-9.0	95	-9.4	87	-5.6	0.0023	0.0006
Week 2	94	-12.8	99	-13.7	92	-7.7	<0.0001	<0.0001
Week 3	96	-13.9	99	-15.0	92	-8.1	<0.0001	<0.0001
Week 4[d]	96	-14.2	99	-16.5	92	-8.2	<0.0001	<0.0001
Treatment Difference at Week 4 [95% CI]							-5.99 [-8.49 to -3.50]	-8.26 [-10.7 to -5.77]
OC								
Week 1	92	-9.0	95	-9.4	87	-5.6	0.0023	0.0006
Week 2	82	-12.8	87	-14.7	81	-8.3	0.0004	<0.0001
Week 3	83	-14.5	75	-16.6	74	-8.9	<0.0001	<0.0001
Week 4[d]	78	-15.0	75	-17.1	67	-9.2	<0.0001	<0.0001
Treatment Difference at Week 4 [95% CI]							-5.81 [-8.51 to -3.12)	-7.92 [-10.6 to -5.20]

vs = versus.

[a]The LS means are the adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and term for treatment. A negative LS mean indicated improvement.

[b]The p-values were derived from Student's t tests on estimates of treatment comparisons which were based on LS means.

[c]For baseline, N and Mean are provided.

[d]Primary endpoint.

Secondary Variables:
No any secondary variables were key secondary variable.

Percentage of Subjects Responding to Treatment (≥ 50% reduction from Baseline in YMRS Total Score)

The percentage of subjects responding to treatment, defined as those having a ≥ 50% reduction from Baseline in YMRS Total Score. Both the aripiprazole 10 mg and 30 mg arms had significantly higher percentages of responders compared to the placebo arm at every treatment week during the Acute Phase. At Week 4 (end of the Acute Phase), the percentages of responders using LOCF were 44.79% (43/96 subjects), 63.64% (63/99 subjects), and 26.09% (24/92 subjects) in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0074$ for 10 mg versus placebo [95% CI = 5.01 to 32.40] and $p < 0.0001$ for 30 mg versus placebo [95% CI = 23.41 to 51.68]). OC analyses data were consistent with findings using LOCF.

Change from Baseline in Children's Global Assessment Scale (CGAS) Score

Both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm in the change from baseline in CGAS Score at the end of the Acute Phase (Week 4) using the LOCF data set. At Week 4, the mean changes from baseline using LOCF were 15.1, 17.3, and 5.8 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively. The treatment effect in mean change from baseline at Week 4 was 9.30 (95% CI = 5.77 to 12.84; $p < 0.0001$) for the aripiprazole 10 mg arm and 11.51 (95% CI = 7.99 to 15.03; $p < 0.0001$) for the aripiprazole 30 mg arm using LOCF. OC analyses data were consistent with findings using LOCF.

Change from Baseline in Clinical Global Impression – Bipolar Version (CGI-BP) Severity Score

Both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm in the change from baseline in CGI-BP severity score for mania at the end of the Acute Phase (Week 4) using the LOCF data set. At Week 4, the mean changes from baseline using LOCF were −1.6, −2.1, and −0.8 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p < 0.0001$ for 10 mg versus placebo and for 30 mg versus placebo). The treatment effect in mean change from baseline at Week 4 was −0.81 (95% CI = −1.15 to −0.48) for the aripiprazole 10 mg arm and −1.26 (95% CI = −1.59 to −0.93) for the aripiprazole 30 mg arm using LOCF. OC analyses data were consistent with findings using LOCF.

6.1.4.6 Subgroup Analysis

Subgroup analyses on the mean change from baseline to endpoint in YMRS total score for gender and race were performed for Study 31-03-240 using LOCF and OC database. Since the age range in this study was narrow, no age groups analyses were performed. The efficacy results from each subgroup were very similar, no any unexpected trend was found.

6.1.5 Clinical Microbiology

Not applicable for this submission.

6.1.6 Efficacy Conclusions

Aripiprazole was effective for the treatment of child and adolescent subjects (ages 10 to 17 years) with bipolar I disorder, manic or mixed episode with or without psychotic features, at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared to placebo in the primary efficacy endpoint, mean change in YMRS Total Score at Week 4 (LOCF). Statistically significant improvements were seen as early as Week 1 for both doses and continued through Week 4 (LOCF).

Under FDAMA, 1997, adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. Aripiprazole has been approved for treatment of acute manic and mixed episodes associated bipolar disorder (September 2004) in adult population. Therefore, the efficacy data from Study 31-03-240 are thought to provide sufficient evidence of efficacy in treatment of acute manic and mixed episodes associated with bipolar disorder in child/adolescent population.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The integrated safety review for this submission is mainly based on all safety data from Study 03-21-240. It is noteworthy that the completion rate of the Extension Phase of this study was very low, overall 23%. Therefore, the comparisons of safety data between treatment groups may be biased. The safety data from Study 31-03-241, an open-label, 6-month safety and tolerability study were also reviewed to assess deaths, serious or unexpected AEs and the effect on growth of child/adolescent population. The database used for this review includes safety reports from each individual study, pertinent .xpt files and narrative summaries.

Since marketing of aripiprazole began in Nov. 2, 2002, its safety profile has been generally well characterized, especially in adult population. The safety review from this submission did not find any unexpected serious adverse events and the patterns of common adverse events of aripiprazole remained consistent with current labeling.

The frequencies of AEs due to all causalities are summarized in Table 7.

Table 7 Summary of Adverse Events (Study 31-03-240)

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)

7.1.1 Extent of Exposure

A total of 197 subjects were exposed to aripiprazole: 98 in the 10 mg arm, with an average dose of 8.6 mg overall (8.3 mg in the Acute Phase and 9.3 mg in the Extension Phase), and 99 in the 30 mg arm, with an average dose of 22.1 mg (19.5 in the Acute Phase and 27.5 in the Extension Phase). The numbers of subjects exposed to study drug for 22 to 28 days were 84/98 (85.7%) in the aripiprazole 10 mg arm at an average dose of 9.5 mg; 77/99 (77.8%) in the aripiprazole 30 mg arm at an average dose of 28.5 mg; and 70/99 (70.7%) in the placebo arm. The numbers of subjects exposed to study drug for 183 to 210 days (26 to 30 weeks) were 34/98 (34.7%) in the aripiprazole 10 mg arm at an average dose of 9.4 mg; 23/99 (23.2%) in the aripiprazole 30 mg arm at an average dose of 26.6 mg; and 13/99 (13.1%) in the placebo arm.

In Study 03-21-241, a total of 325 subjects were exposed to aripiprazole: 239 adolescent subjects with schizophrenia (who had completed Study 31-03-0239) at average daily doses ranging from 5.2 mg to 20.7 mg, and 86 children and adolescent subjects with bipolar I disorder (who had withdrawn from the double-blind extension phase of Study 31-03-240) at average daily doses ranging from 4.9 mg to 17.7 mg. The average daily dose ranges were slightly lower in the subpopulation with bipolar I disorder. The average daily dose overall during the study was 16.3 mg. The percentage of subjects exposed to study drug for ≥ 182 days (at an average daily dose of 16.8 mg) was 50.8% (165/325).

To date, aripiprazole has been evaluated for safety in 514 pediatric patients (10 to 17 yrs) in the Abilify pediatric program in response to the PWR. This represents approximately 205 patient-years of exposure to oral aripiprazole. A total of 278 patients were treated with oral aripiprazole of 10 mg-30 mg for at least 180 days.

7.1.2 Deaths

No deaths were reported in this study.

7.1.3 Other Serious Adverse Events

The incidence of SAEs in the Acute Phase and the entire study is summarized in Table 8. A total of 5/98 (5.1%) subjects in the aripiprazole 10 mg arm, 2/99 (2.0%) in the aripiprazole 30 mg arm, and 5/97 (5.2%) in the placebo arm experienced SAEs during the Acute Phase, the majority of which were moderate or severe in intensity. The most commonly reported SAEs during the entire study were bipolar disorder (9/294 subjects; 3.1% overall) and bipolar I disorder (3/294 subjects, 1.0% overall).

Other SAEs reported during the Acute Phase were fatigue (1 subject in the 10 mg arm), accidental overdose (1 subject in the 10 mg arm), grand mal convulsion (1 subject in the 10 mg arm, secondary to alcohol and cocaine overdose), aggression (2 subjects in the 10 mg arm), oppositional defiant disorder (1 subject in the aripiprazole 10 mg arm), suicidal ideation (1 subject in the 10 mg arm), and respiratory arrest (1 subject in the 10 mg arm, secondary to alcohol and cocaine overdose).

Table 8 Summary of Serious Adverse Events (Study 31-03-240)

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
Class and MedDRA Preferred Term								
Total subjects with at least one SAE	5 (5.1)	2 (2.0)	5 (5.2)	12 (4.1)	5 (5.1)	7 (7.1)	6 (6.2)	18 (6.1)
General Disorders and Administration Site Conditions								
Fatigue	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Injury, Poisoning, and Procedural Complications								
Accidental overdose	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Nervous System Disorders								
Grand mal convulsion	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychiatric Disorders								
Aggression	2 (2.0)	0 (0.0)	0 (0.0)	2 (0.7)	2 (2.0)	0 (0.0)	0 (0.0)	2 (0.7)
Bipolar disorder	0 (0.0)	2 (2.0)	4 (4.1)	6 (2.0)	0 (0.0)	5 (5.1)	4 (4.1)	9 (3.1)
Bipolar I Disorder	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)	0 (0.0)	2 (2.0)	1 (1.0)	3 (1.0)
Libido increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Mania	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Oppositional defiant disorder	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Suicidal ideation	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Respiratory, Thoracic, and Mediastinal Disorders								
Respiratory arrest	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)

Overall, 6 subjects experienced SAEs resulting in discontinuation of study medication: in the aripiprazole 10 mg arm, 1 subject was discontinued due to suicidal ideation, and 1 subject was discontinued due to aggression and fatigue; in the aripiprazole 30 mg arm, 3 subjects were discontinued due to bipolar disorder; and in the placebo arm, 1 subject was discontinued due to bipolar I disorder.

7.1.4 Dropouts and Other Significant Adverse Events

7.1.4.1 Overall profile of dropouts

Aripiprazole treatment was associated with higher dropouts due to AEs. During the Acute Phase, a total of 16/294 (5.4%) subjects discontinued study medication due to a TEAE: 6/98 (6.1%) in the aripiprazole 10 mg arm, 8/99 (8.1%) in the aripiprazole 30 mg arm, and 2/97 (2.1%) in the placebo arm. During the entire study, a total of 30/294 (10.2%) subjects discontinued study medication due to a TEAE: 9/98 (9.2%) in the aripiprazole 10 mg arm, 19/99 (19.2%) in the aripiprazole 30 mg arm, and 2/97 (2.1%) in the placebo arm. The majority of the events were moderate to severe in intensity.

7.1.4.2 Adverse events associated with dropouts

The incidences TEAEs resulting in discontinuation of study medication are summarized in Table 9. The most commonly reported TEAEs resulting in discontinuation of study medication (reported by more than 1 subject overall) during the Acute Phase were extrapyramidal disorder (3 subjects in the aripiprazole 30 mg arm), sedation (2 subjects in the aripiprazole 10 mg arm), fatigue (2 subjects in the aripiprazole 10 mg arm), and bipolar disorder (2 subjects in the aripiprazole 30 mg arm). Other TEAEs resulting in discontinuation of study medication during the Acute Phase (in 1 subject each) were: akathisia, aggression, and suicidal ideation in the aripiprazole 10 mg arm; vomiting, dystonia, and somnolence in the aripiprazole 30 mg arm; and anxiety and bipolar I disorder in the placebo arm.

Additional TEAEs resulting in discontinuation of study medication during the Extension Phase were: increased weight, dystonia, and depression in 1 additional subject each in the aripiprazole 10 mg arm; and somnolence (3 additional subjects), fatigue (2 additional subjects), bipolar disorder (2 additional subjects), increased weight (1 additional subject), extrapyramidal disorder (1 additional subject), grand mal convulsion (1 subject), and sedation (1 additional subject) in the aripiprazole 30 mg arm.

Table 9 Incidence of Discontinuation Due to Adverse Events (Study 31-03-240)

Number of:	Acute Phase					Acute + Extension Phases				
	Arip 10 mg n (%)	Arip 30 mg n (%)	Total Arip n (%)	Placebo n (%)	Total n (%)	Arip 10 mg n (%)	Arip 30 mg n (%)	Total Arip n (%)	Placebo n (%)	Total n (%)
Subjects treated, N	98	99	197	97	294	98	99	197	97	294
Class and MedDRA Preferred Term										
Total subjects discontinued due to AEs	6 (6.1)	8 (8.1)	14 (7.1)	2 (2.1)	16 (5.4)	9 (9.2)	19 (19.2)	28 (14.2)	2 (2.1)	30 (10.2)
Gastrointestinal Disorders										
Vomiting	0 (0.0)	1 (1.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)	1 (1.0)	1 (0.5)	0 (0.0)	1 (0.3)
General Disorders and Administration Site Conditions										
Fatigue	2 (2.0)	0 (0.0)	2 (1.0)	0 (0.0)	2 (0.7)	2 (2.0)	2 (2.0)	4 (2.0)	0 (0.0)	4 (1.4)
Investigations										
Weight increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.0)	2 (1.0)	0 (0.0)	2 (0.7)
Nervous System Disorders										
Akathisia	1 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	1 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
Dystonia	0 (0.0)	1 (1.0)	1 (0.5)	0 (0.0)	1 (0.3)	1 (1.0)	1 (1.0)	2 (1.0)	0 (0.0)	2 (0.7)
Extrapyramidal disorder	0 (0.0)	3 (3.0)	3 (1.5)	0 (0.0)	3 (1.0)	0 (0.0)	4 (4.0)	4 (2.0)	0 (0.0)	4 (1.4)
Grand mal convulsion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)	0 (0.0)	1 (0.3)
Sedation	2 (2.0)	0 (0.0)	2 (1.0)	0 (0.0)	2 (0.7)	2 (2.0)	1 (1.0)	3 (1.5)	0 (0.0)	3 (1.0)
Somnolence	0 (0.0)	1 (1.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)	4 (4.0)	4 (2.0)	0 (0.0)	4 (1.4)
Psychiatric Disorders										
Aggression	1 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	1 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Bipolar disorder	0 (0.0)	2 (2.0)	2 (1.0)	0 (0.0)	2 (0.7)	0 (0.0)	4 (4.0)	4 (2.0)	0 (0.0)	4 (1.4)
Bipolar I Disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
Suicidal ideation	1 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	1 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)

Arip = Aripiprazole

7.1.4.3 Other significant adverse events

No other significant adverse events were reported in Study 31-03-240.

7.1.5 Other Search Strategies

No other search strategies were performed in Study 31-03-240.

7.1.6 Common Adverse Events

7.1.6.1 Eliciting adverse events data in the development program

An AE was defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it was considered drug-related by the investigator. An AE was considered serious if it was fatal; life-threatening; persistently or significantly disabling or incapacitating; required in-subject hospitalization or prolonged hospitalization; a congenital anomaly/birth defect; or other medically significant event that, based upon appropriate medical judgment, may have jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above.

In order to avoid bias in eliciting AEs, subjects were asked the following nonleading question: "How have you felt since your last visit?" Investigators were required to record all AEs (serious and nonserious) reported by the subject on the CRFs and source documents provided by the sponsor.

7.1.6.2 Appropriateness of adverse event categorization and preferred terms

All AEs were coded from verbatim terms to System Organ Class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA), Version 9.1.

7.1.6.3 Incidence of common adverse events

The percentage of subjects who experienced at least one TEAE was slightly higher in the aripiprazole arms than in the placebo arm. During the Acute Phase, a total of 738 TEAEs were reported by 204 subjects: 72/98 (73.5%) in the aripiprazole 10 mg arm, 75/99 (75.8%) in the aripiprazole 30 mg arm, and 57/97 (58.8%) in the placebo arm. During the entire study, a total of 906 TEAEs were reported by 226 subjects: 78/98 (79.6%) in the aripiprazole 10 mg arm, 84/99 (84.8%) in the aripiprazole 30 mg arm, and 64/97 (66.0%) in the placebo arm. The majority of TEAEs in all treatment arms were mild to moderate in severity.

During the Acute Phase, the most common TEAEs reported at an incidence rate of ≥ 5% in the aripiprazole 10 mg arm were somnolence (19.4%), headache (17.3%), fatigue (13.3%), extrapyramidal disorder (12.2%), nausea (9.2%), vision blurred (8.2%), vomiting (8.2%), akathisia (8.2%), decreased appetite (6.1%), and dizziness (5.1%). The most common TEAEs reported at an incidence rate of ≥ 5% during the Acute Phase in the aripiprazole 30 mg arm were extrapyramidal disorder (27.3%), somnolence (26.3%), headache (19.2%), nausea (12.1%), akathisia (11.1%), fatigue (9.1%), vision blurred (8.1%), salivary hypersecretion (8.1%), vomiting (7.1%), increased appetite (5.1%), dizziness (5.1%), upper abdominal pain (5.1%), and dystonia (5.1%).

During the Acute Phase, there appeared to be a general trend of increasing incidence across the treatment groups for the commonly reported TEAEs of nausea, salivary hypersecretion, akathisia, extrapyramidal disorder, somnolence, dystonia, and headache, with the highest incidence in the aripiprazole 30 mg arm. In addition, a greater incidence of the following TEAEs was noted in the aripiprazole arms compared to the placebo arm: blurred vision, diarrhea, and dizziness.

7.1.6.4 Common adverse event tables

Table 10 summarizes the most commonly reported TEAEs (by ≥ 5% incidence in any treatment arm) for the Acute Phase and the entire study (Acute + Extension Phases).

Table 10 Most Commonly Reported TEAEs by 5% or Greater Incidence (Study 31-03-240)

Number of:	Acute Phase					Acute + Extension Phases				
	Arip 10 mg n (%)	Arip 30 mg n (%)	Total Arip n (%)	Placebo n (%)	Total n (%)	Arip 10 mg n (%)	Arip 30 mg n (%)	Total Arip n (%)	Placebo n (%)	Total n (%)
Subjects treated, N	98	99	197	97	294	98	99	197	97	294
Class and MedDRA Preferred Term										
Total subjects with at least one TEAE	72 (73.5)	75 (75.8)		57 (58.8)	204 (69.4)	78 (79.6)	84 (84.8)		64 (66.0)	226 (76.9)
Eye Disorders										
Vision Blurred	8 (8.2)	8 (8.1)	16 (8.1)	0 (0.0)	16 (5.4)	10 (10.2)	8 (8.1)	18 (9.1)	1 (1.0)	19 (6.5)
Gastrointestinal Disorders										
Abdominal pain, upper	4 (4.1)	5 (5.1)	9 (4.6)	3 (3.1)	12 (4.1)	9 (9.2)	5 (5.1)	14 (7.1)	3 (3.1)	17 (5.8)
Diarrhea	4 (4.1)	4 (4.0)	8 (4.1)	0 (0.0)	8 (2.7)	4 (4.1)	5 (5.1)	9 (4.6)	0 (0.0)	9 (3.1)
Nausea	9 (9.2)	12 (12.1)	21 (10.7)	4 (4.1)	25 (8.5)	13 (13.3)	14 (14.1)	27 (13.7)	5 (5.2)	32 (10.9)
Salivary hypersecretion	3 (3.1)	8 (8.1)	11 (5.6)	0 (0.0)	11 (3.7)	3 (3.1)	8 (8.1)	11 (5.6)	0 (0.0)	11 (3.7)
Stomach discomfort	2 (2.0)	4 (4.0)	6 (3.0)	2 (2.1)	8 (2.7)	2 (2.0)	6 (6.1)	8 (4.1)	2 (2.1)	10 (3.4)
Vomiting	8 (8.2)	7 (7.1)	15 (7.6)	9 (9.3)	24 (8.2)	13 (13.3)	8 (8.1)	21 (10.7)	9 (9.3)	30 (10.2)
General Disorders and Administration Site Conditions										
Fatigue	13 (13.3)	9 (9.1)	22 (11.2)	4 (4.1)	26 (8.8)	18 (18.4)	12 (12.1)	30 (15.2)	4 (4.1)	34 (11.6)
Infections and Infestations										
Nasopharyngitis	4 (4.1)	3 (3.0)	7 (3.6)	1 (1.0)	8 (2.7)	7 (7.1)	3 (3.0)	10 (5.1)	3 (3.1)	13 (4.4)
Upper respiratory tract infection	3 (3.1)	2 (2.0)	5 (2.5)	3 (3.1)	8 (2.7)	8 (8.2)	6 (6.1)	14 (7.1)	3 (3.1)	17 (5.8)
Investigations										
Weight increased	4 (4.1)	3 (3.0)	7 (3.6)	1 (1.0)	8 (2.7)	8 (8.2)	5 (5.1)	13 (6.6)	3 (3.1)	16 (5.4)
Metabolism and Nutrition Disorders										
Decreased appetite	6 (6.1)	3 (3.0)	9 (4.6)	3 (3.1)	12 (4.1)	7 (7.1)	4 (4.0)	11 (5.6)	3 (3.1)	14 (4.8)
Increased appetite	2 (2.0)	5 (5.1)	7 (3.6)	3 (3.1)	10 (3.4)	8 (8.2)	8 (8.1)	16 (8.1)	3 (3.1)	19 (6.5)
Musculoskeletal and Connective Tissue Disorders										
Back pain	2 (2.0)	2 (2.0)	4 (2.0)	1 (1.0)	5 (1.7)	5 (5.1)	3 (3.0)	8 (4.1)	2 (2.1)	10 (3.4)
Nervous System Disorders										
Akathisia	8 (8.2)	11 (11.1)	19 (9.6)	2 (2.1)	21 (7.1)	9 (9.2)	13 (13.1)	22 (11.2)	2 (2.1)	24 (8.2)
Dizziness	5 (5.1)	5 (5.1)	10 (5.1)	1 (1.0)	11 (3.7)	7 (7.1)	5 (5.1)	12 (6.1)	1 (1.0)	13 (4.4)
Dystonia	0 (0.0)	5 (5.1)	5 (2.5)	0 (0.0)	5 (1.7)	2 (2.0)	5 (5.1)	7 (3.6)	0 (0.0)	7 (2.4)
Extrapyramidal disorder	12 (12.2)	27 (27.3)	39 (19.8)	3 (3.1)	42 (14.3)	12 (12.2)	28 (28.3)	40 (20.3)	3 (3.1)	43 (14.6)
Headache	17 (17.3)	19 (19.2)	36 (18.3)	16 (16.5)	52 (17.7)	20 (20.4)	23 (23.2)	43 (21.8)	18 (18.6)	61 (20.7)
Somnolence	19 (19.4)	26 (26.3)	45 (22.8)	3 (3.1)	48 (16.3)	24 (24.5)	27 (27.3)	51 (25.9)	3 (3.1)	54 (18.4)
Psychiatric Disorders										
Anxiety	4 (4.1)	1 (1.0)	5 (2.5)	3 (3.1)	8 (2.7)	5 (5.1)	1 (1.0)	6 (3.0)	3 (3.1)	9 (3.1)
Bipolar disorder	0 (0.0)	3 (3.0)	3 (1.5)	5 (5.2)	8 (2.7)	0 (0.0)	6 (6.1)	6 (3.0)	5 (5.2)	11 (3.7)
Insomnia	4 (4.1)	1 (1.0)	5 (2.5)	1 (1.0)	6 (2.0)	6 (6.1)	1 (1.0)	7 (3.6)	2 (2.1)	9 (3.1)
Reproductive System and Breast Disorders										
Dysmenorrhea	2 (2.0)	0 (0.0)	2 (1.0)	0 (0.0)	2 (0.7)	5 (5.1)	0 (0.0)	5 (2.5)	2 (2.1)	7 (2.4)
Respiratory, Thoracic, and Mediastinal Disorders										
Cough	1 (1.0)	1 (1.0)	2 (1.0)	4 (4.1)	6 (2.0)	7 (7.1)	1 (1.0)	8 (4.1)	4 (4.1)	12 (4.1)
Nasal congestion	3 (3.1)	2 (2.0)	5 (2.5)	3 (3.1)	8 (2.7)	10 (10.2)	3 (3.0)	13 (6.6)	3 (3.1)	16 (5.4)
Pharyngolaryngeal pain	2 (2.0)	1 (1.0)	3 (1.5)	3 (3.1)	6 (2.0)	5 (5.1)	2 (2.0)	7 (3.6)	3 (3.1)	10 (3.4)

Arip = Aripiprazole

7.1.6.5 Identifying common and drug-related adverse events

Common adverse events were identified by that the occurrence rate was at least 2% or more in treatment arms.

Any event with onset after the first dose of aripiprazole or any event which was ongoing from baseline and became serious, worsened, was classified as related to study drug, or resulted in death, discontinuation, interruption or reduction of dose was considered to be treatment-emergent.

7.1.6.6 Additional analyses and explorations

Extrapyramidal Symptom (EPS) Events

The incidence of any extrapyramidal event showed a dose-response relationship: aripiprazole 30 mg group had highest incidence (34.3% in the Acute Phase and 36.3% in the entire study), followed by aripiprazole 10 mg group (17.3% in the Acute Phase and 20.4% in the entire study). In the placebo group, the incidence of any extrapyramidal event was 5.1% in both the Acute Phase and the entire study.

The most commonly reported EPS-related symptom during the study was Parkinsonism events (21.8% of the combined aripiprazole group and 4.1% of the placebo group in the Acute Phase, 22.8% of the combined aripiprazole group and 4.1% of the placebo group in the entire study).

Akathisia events occurred in 10.1% of the combined aripiprazole group and 2.0% of the placebo group during the Acute Phase. During the entire study, akathisia events were reported in 11.6% of the combined aripiprazole group and 3% in the placebo group.

Table 11 summaries TEAEs associated with extrapyramidal symptoms.

Table 11 Treatment-Emergent Adverse Events Associated with Extrapyramidal Symptoms (Study 31-03-240)

Extrapyramidal Events	Acute Phase				Acute + Extension Phases			
	Aripiprazole 10 mg (N = 98) n (%)	Aripiprazole 30 mg (N = 99) n (%)	Total Aripiprazole (N = 197) n (%)	Placebo (N = 97) n (%)	Aripiprazole 10 mg (N = 98) n (%)	Aripiprazole 30 mg (N = 99) n (%)	Total Aripiprazole (N = 197) n (%)	Placebo (N = 97) n (%)
Dystonic events	0 (0.0)	7 (7.0)	7 (3.5)	2 (2.0)	2 (2.0)	8 (8.0)	10 (5.0)	2 (2.0)
Parkinsonism events	14 (14.2)	29 (29.2)	43 (21.8)	4 (4.1)	15 (15.3)	30 (30.3)	45 (22.8)	4 (4.1)
Dyskinetic events	2 (2.0)	0 (0.0)	2 (1.0)	0 (0.0)	2 (2.0)	0 (0.0)	2 (1.0)	0 (0.0)
Residual events	1 (1.0)	1 (1.0)	2 (1.0)	0 (0.0)	1 (1.0)	1 (1.0)	2 (1.0)	0 (0.0)
Any extrapyramidal event[a]	17 (17.3)	34 (34.3)	51 (25.8)	5 (5.1)	20 (20.4)	36 (36.3)	56 (28.4)	5 (5.1)
Akathisia events	8 (8.1)	12 (12.1)	20 (10.1)	2 (2.0)	9 (9.1)	14 (14.1)	23 (11.6)	3 (3.0)

7.1.7 Less Common Adverse Events

No less common adverse events of significant concern were identified in Study 31-03-240.

7.1.8 Laboratory Findings

7.1.8.1 Overview of laboratory testing in the development program

Routine safety laboratory including hemotology, serum chemistry, and urinalysis were conducted during the study. Other laboratory tests including serum insulin, fasting insulin, and prolactin were also performed. Mean changes from baseline to endpoint, treatment-emergent abnormalities at any time and treatment-emergent potentially clinically significant abnormalities for each laboratory analyte were analyzed separately.

7.1.8.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The laboratory data from Study 21-03-240 (a placebo-controlled study) were reviewed in detail in this section of the integrated safety review. The laboratory data from Study 21-03-241 (an open-labeled 6 month study) were examined to detect rare, unexpected or serious clinical significant laboratory abnormalities.

7.1.8.3 Standard analyses and explorations of laboratory data

7.1.8.3.1 Analyses focused on measures of central tendency

No clinically relevant mean changes were observed for any of the serum chemistry laboratory tests, hematology, urinalysis laboratory tests, and insulin or fasting insulin levels.

Mean decreases in prolactin levels relative to baseline were observed in the two aripiprazole treatment arms in male subjects, and in both of the aripiprazole arms and the placebo arm in female subjects. The mean changes from baseline to the last visit in prolactin levels were −2.58 ng/mL, −3.39 ng/mL, and 0.72 ng/mL in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms, respectively, in male subjects; and −5.39 ng/mL, −1.41 ng/mL, and −1.79 ng/mL, respectively, for female subjects.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Increased creatine phosphokinase abnormalities were reported as TEAEs in 1 subject each in the placebo and aripiprazole 10 mg arms (1.0%) and 4 subjects in the aripiprazole 30 mg arm (4.0%) during the entire study period. Other TEAEs during the entire study period include increased AST (1, arip 30 mg), increased cholesterol (2, arip 10 mg), increased blood insulin (2, arip 10 mg), increased blood potassium (1, arip 10 mg), increased triglycerides (1, placebo), increased HbA1c (1, arip 10 mg), and liver function test abnormal (1, arip 10 mg). There were no obvious dose-related trends observed in the serum chemistry test abnormalities reported as TEAEs.

Prolactin Levels

The incidence of low prolactin levels relative to baseline (less than or equal to 3 ng/dL in females and less than or equal to 2 ng/dL in males) during the Acute Phase and the entire study was greatest in the aripiprazole 30 mg arm (39.3% in the Acute phase and 44.6% in the entire study), followed by the aripiprazole 10 mg arm (25.3% in the Acute Phase and 36.6% in the entire study), and then by the placebo arm (2.4% in the Acute Phase and 2.3% in the entire study).

A higher proportion of males experienced decreased prolactin levels than females in both the Acute Phase and in the entire study, and across all treatment groups. The clinical significance of decrease in prolactin level is unclear.

An overall low incidence (around 1%) of clinically significant hyperprolactinemia was observed in this study.

7.1.8.3.3 Marked outliers and dropouts for laboratory abnormalities

The overall incidence of potentially clinically significant individual laboratory values was low (< 2% of subjects) for all analytes during the Acute Phase and for all analytes except CPK during the entire study period. The incidence of potentially clinically significant CPK values during the Acute Phase was 1.1% (1 subject), 3.4% (3 subjects), and 1.2% (1 subject) in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms, respectively. During the entire study period, the incidence of potentially clinically significant CPK values was 5.4% (5 subjects), 7.6% (7 subjects), and 2.3% (2 subjects) in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms, respectively. Overall, no clinically meaningful trends were observed for any of the potentially clinically significant laboratory test abnormalities.

None of laboratory abnormalities were reported as SAEs or resulted in discontinuation of study medication.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were deemed necessary for these studies.

7.1.8.5 Special assessments

No special assessments were warranted in these studies.

7.1.9 Vital Signs

7.1.9.1 Overview of vital signs testing in the development program

The potential treatment effect on mean change from baseline to endpoint, and on treatment-emergent potentially clinically significant abnormalities in vital signs including standing and supine blood pressure, standing and supine heart rate, body temperature and weight were summarized and assessed across treatment groups.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The vital sign data from Study 21-03-240 (a placebo-controlled study) were reviewed in detail in this section of the integrated safety review. The vital sign data from Study 21-03-241 (an open-labeled 6 month study) were examined to detect rare, unexpected or serious clinical significant vital sign abnormalities.

7.1.9.3 Standard analyses and explorations of vital signs data

7.1.9.3.1 Analyses focused on measures of central tendencies

No clinically relevant mean changes from baseline were observed in vital signs parameters.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no clinically notable trends in the incidence of potentially clinically significant vital sign abnormalities.

The following abnormal vital sign findings were reported as TEAEs: palpitation (1, placebo), tachycardia (1, placebo), pyrexia (4 each in the arip. 10 mg and 30 mg), heart rate increased (2, arip. 30 mg), weight decreased (1, placebo), weight increased (8, arip. 10 mg; 5, arip. 30 mg; and 3, placebo), hot flush (1, placebo), and orthostatic hypotension (1 arip. 10 mg).

7.1.9.3.3 Marked outliers and dropouts for vital sign abnormalities

Significant orthostatic changes (systolic BP decreased ≥ 20 mmHg accompanied by increased HR ≥ 25 bpm) were observed in 1 subject in the placebo arm during the Acute Phase and 2 (2.1%) subjects each in the aripiprazole 10 mg arm and the placebo arm during the entire study.

Increased weight resulted in discontinuation of study medication in 1 subject each in the aripiprazole 10 mg and 30 mg arms during the Extension Phase.

7.1.9.4 Additional analyses and explorations

Metabolic Syndrome Evaluation

The mean changes from baseline in metabolic syndrome parameters, including fasting triglycerides, fasting HDL-C levels, fasting glucose levels, waist circumference, BMI, z-scores, standing and supine blood pressures were assessed by visit and gender. Overall, no clinically meaningful changes from baseline were observed in any of the metabolic syndrome evaluation parameters for males or females.

The frequencies of clinically significant metabolic syndrome abnormalities for fasting triglycerides, fasting HDL-C levels, fasting glucose levels, waist circumference, BMI and standing and supine blood pressures were also assessed by visit and gender. Overall at the last visit, no clinically meaningful trends were observed in the increasing incidences of abnormalities for fasting triglyceride levels, fasting HDL-C levels, fasting glucose levels, waist circumference, BMI, supine systolic or diastolic BP, and standing systolic and diastolic BP.

The frequencies of fasting cholesterol levels of ≥ 170 mg/dL were 40.5%, 43.1%, and 22.2% in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms, respectively, for the Acute Phase, and the incidences were 39.3%, 48.1%, and 26.9% over the entire study period respectively.

There was a greater incidence of weight gain at the end of the study (Last Visit). The mean changes in weight at the end of the Acute Phase were 0.55, 0.90, and 0.54 kg for the aripiprazole 10 mg, 30 mg, and placebo arms, respectively. The mean changes in weight at the end of the study (Last Visit) were 3.20, 2.85, and 0.98 kg for the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0002$ and $p = 0.0019$ for the 10 mg and 30 mg arms, respectively, versus placebo).

At the last visit, the percentages of subjects who experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline) were 35.8% in the aripiprazole 10 mg arm, 29.2% in the aripiprazole 30 mg arm, and 9.8% in the placebo arm. The differences from placebo in the incidence of potentially clinically significant weight gain were statistically significant at the last visit for both the aripiprazole 10 mg arm and 30 mg arm ($p < 0.0001$ and $p = 0.0009$, respectively).

Overall, the mean changes from baseline for weight z-scores and BMI z-scores for each visit were generally within 0.5 SD of the population for all three treatment arms, and the changes from baseline were negligible. At the last visit, the mean change (SD) in weight z-score was 0.13 (0.35) with a range of −0.78 to 1.48 in the aripiprazole 10 mg arm; 0.17 (0.41) with a range of −1.09 to 2.20 in the aripiprazole 30 mg arm; and 0.01 (0.20) with a range of −0.49 to 0.73 in the placebo arm. At the last visit, the mean change (SD) in BMI z-score was 0.12 (0.41) with a range of −1.42 to 1.61 in the aripiprazole 10 mg arm; 0.19 (0.51) with a range of −1.05 to 2.79 in the aripiprazole 30 mg arm; and 0.01 (0.24) with a range of −0.59 to 1.06 in the placebo arm.

Very few subjects (4, arip. 10 mg; 5, arip 30 mg; and 2, placebo) had a shift in weight z-score from normal (< 95th percentile) at Baseline to abnormal (weight z-score ≥ 95th percentile) at the Last Visit. Therefore, although weight changes occurred, they were not clinically relevant based upon z-scores and shift tables.

7.1.10 Electrocardiograms (ECGs)

7.1.10.1 Overview of ECG testing in the development program, including brief review of preclinical results

Mean changes, treatment-emergent ECG abnormalities, and treatment-emergent potentially clinically significant ECG abnormalities were examined and compared across treatment groups. No clinical meaningful ECG abnormalities were observed.

7.1.10.2 Selection of studies and analyses for overall drug-control comparisons

The ECG data from Study 21-03-240 (a placebo-controlled study) were reviewed in detail in this section of the integrated safety review. The ECG data from Study 21-03-241 (an open-labeled 6 month study) were examined to detect rare, unexpected or serious clinical significant ECG abnormalities.

7.1.10.3 Standard analyses and explorations of ECG data

7.1.10.3.1 Analyses focused on measures of central tendency

Although there were statistically significant differences compared to placebo in treatment comparisons for mean change from baseline in some parameters, none of these differences were considered clinically meaningful.

7.1.10.3.2 Analyses focused on outliers or shifts from normal to abnormal

Overall, no clinically meaningful trends were observed for any of the potentially clinically significant changes in ECG parameters.

One subject in the placebo arm experienced bundle branch block that was reported as a TEAE; this event was not considered serious and did not result in discontinuation of study medication.

7.1.10.3.3 Marked outliers and dropouts for ECG abnormalities

None of the ECG abnormalities were reported as SAEs or resulted in discontinuation of study medications.

7.1.10.4 Additional analyses and explorations

No additional analyses or explorations were performed in these studies.

7.1.11 Immunogenicity

Immunogenicity was not studied in these studies.

7.1.12 Human Carcinogenicity

Human carcinogenicity was not studied in these studies.

7.1.13 Special Safety Studies

No special safety studies were deemed necessary.

7.1.14 Withdrawal Phenomena and/or Abuse Potential

Withdrawal phenomena and /or abuse potential were not studied in these studies.

7.1.15 Human Reproduction and Pregnancy Data

No pregnancies were reported in these studies.

7.1.16 Assessment of Effect on Growth

Overall, the mean changes from baseline for weight z-scores and BMI z-scores for each visit in Study 31-03-240 and 31-03-241 were generally within 0.5 SD of the general population for all three treatment arms, and the changes from baseline were negligible. More discussion can be found at section 7.1.9.4 Additional Analyses and Explorations.

7.1.17 Overdose Experience

No aripiprazole overdose experience was reported in these studies.

7.1.18 Postmarketing Experience

Since aripiprazole was approved for marketing in Nov. 2002, it was estimated that 42,170 patients aged 1-20 years have received aripiprazole from 19 Nov. 2002 to 16 Aug. 2003. Aripiprazole naïve patients for whom at least one Abilify prescription had been filled were estimated to be [redacted]. In addition, based on post-marketing safety surveillance information from 423 pediatric aripiprazole spontaneous cases received during the period starting 19-NOV-2002 and ending 09-JAN- 2005, aripiprazole doses ranging from 3.5 mg to 30 mg were reported in pediatric patients ranging from 2.5 to 17 years of age. The pattern of adverse event frequency

seen in the pediatric patients is similar to what has been observed in the adult population, and as such, does not reflect a medically significant deviation from the known profile of aripiprazole.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Study 31-03-240 was a out/in-patient, multi-center, randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in child and adolescent subjects, ages 10 to 17 years, with a diagnosis of bipolar I disorder, manic or mixed episode, with or without psychotic features.

The study included two phases: a 4-week acute treatment phase and a 24-week extension phase. Patients who met inclusion criteria were randomized into one of 3 treatment arms: aripiprazole 10 mg, aripiprazole 30 mg or placebo arm, with a 1:1:1 ratio. Patients who completed 4-week acute treatment phase continued into the extension phase beginning at the same dose taken at the end of the acute phase.

A total of 413 subjects were screened, and 296 subjects were randomized in this study: 98/296 (33.1%) in the aripiprazole 10 mg arm, 99/296 (33.4%) in the aripiprazole 30 mg arm, and 99/296 (33.4%) in the placebo arm. A high overall rate of retention (237/296 [80.1%]) was observed for the Acute Phase and aripiprozole 10 mg arm had the highest completion rate (85.7%, 77.8%, and 76.8% in arip 10 mg, 30 mg and placebo respectively). The retention rates were pretty low in the extension phase: 34.7%, 22.2% and 12.1% in the aripiprozole 10 mg, 30 mg and placebo groups, respectively. Lack of efficacy as determined by investigator and subject withdrew consent are two most common reasons for discontinuation. Adverse experience led to an overall 10.1% of patient discontinuation. Table 3 summarizes the subject disposition in Study 31-03-240.

Table 12 Subject Discontinuation in Study 31-03-240

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)

7.2.1.2 Demographics

The three treatment arms were demographically similar. The majority of subjects were male (159/296, 53.72%), Caucasian (193/296, 65.20%). This distribution is consistent with the distribution of schizophrenic population. Black/African American subjects consist of 21.96% of subjects and Hispanic/Latino subjects accounted for 10.47% of subjects. The mean age was 13.43 years (range, 10.0 to 17.0 years).

Overall, the baseline disease severity was comparable across all treatment arms. The mean Y-MRS Total Score and CDRS-R Suicidal Ideations Score were 30.0 and 1.2, respectively. Mean baseline YMRS Total Scores by treatment group were 29.8, 29.5, and 30.7 in the aripiprazole 10 mg and 30 mg arms and the placebo arm, respectively. A total of 170/296 (57.40%) subjects had received treatment for previous episodes.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies were conducted to evaluate the safety for this submission.

7.2.2.2 Postmarketing experience

See the section 7.1.18 Postmarketing Experience

7.2.2.3 Literature

See the section 8.6 Literature Review

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience was adequate to evaluate the efficacy and safety of aripiprazole in the treatment of child/adolescent bipolar I disorder, manic or mixed episode with or without psychotic features.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No animal and/or in vitro tests were conducted for this submission, nor were the studies were deemed necessary.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing in this submission was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Andre J. Jackson, PhD is the primary clinical pharmacology reviewer. Please refer to his review for pertinent information.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There are no recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

An audit of the Case Report Forms (CRFs), Narrative Summaries and adverse event data listing was conducted for two patients (03240-21-5275 and 03240-913-5119, ~5% of the 49 patients with submitted CRFs), whom I randomly selected from the database from Study 31-03-240. The AE data listings examined were AE0.xpt from Study 31-03-240 datasets. The consistency of AE data across CRFs, Narrative Summaries and AE0.xpt file was examined. An examination of the AE information across these sources for this subject revealed reasonable consistency and completeness.

7.2.9 Additional Submissions, Including Safety Update

Lilly submitted a Safety Update from an ongoing open-label trial, study 31-05-243, on Nov. 8, 2007 to provide additional long-term safety data. The clinical data cut-off date for inclusion of data in this analysis was 21 Jun 2007.

Study 31-05-243 is an ongoing, open-label, multicenter, non-comparativen rollover study designed to continue to provide aripiprazole on a compassionate use basis in doses ranging from

5 to 30 mg to adolescent (13 to 17 years of age) and adult (adolescents who reach 18 during the open-label or double-blind parent studies) subjects with a diagnosis of schizophrenia according to the DSM-IV. This study is intended for countries where aripiprazole is not available through marketed means. Subjects are required to complete Study 31-03-241 in order to be eligible for the current rollover study. Study 31-03-241 was a multicenter, open-label study that provided up to 6 months of aripiprazole for subjects completing Study 31-03-239, a randomized, comparative study in which adolescents with a DSM-IV diagnosis of schizophrenia received double-blind treatment (aripiprazole or placebo) for 6 weeks.

As of the clinical data cut-off date of 21 Jun 2007, long-term safety data were available from 85 adolescent and young adult subjects with schizophrenia that received oral aripiprazole in Study 31-05-243. Nearly 75% of the subjects in the safety evaluation received aripiprazole for more than 26 weeks in the rollover study. Subjects received an additional 26 to 32 weeks of aripiprazole in the parent studies before enrolling in Study 31-05-243. Therefore, the actual cumulative exposure to aripiprazole may exceed 1 year for the majority of subjects included in this update. Subjects received an average aripiprazole dose of 17.2 mg daily, ranging from 5.0 mg to 30.0 mg.

The safety profile of aripiprazole observed for the ongoing study is consistent with the known current profile in the adolescent and adult schizophrenia populations observed in the post-marketing arena and in clinical trials. No new signals were observed.

No deaths were reported in the study. Five (5.9%) subjects reported a total of 6 SAEs. Two (2.4%) of the SAE reports were for suicide attempt, reported as unrelated or not likely related to aripiprazole treatment. Aripiprazole was generally safe and well tolerated at daily doses of 5 to 30 mg in adolescents and young adults with schizophrenia in this analysis, with the majority of TEAEs reported as mild or moderate. The most common TEAEs (≥ 5% of subjects), irrespective of causality, were influenza (7.1%) and vomiting (5.9%). Extrapyramidal and akathisia events were reported by 5.8% and 2.3% of subjects, respectively.

No clinically meaningful changes in mean QT_c intervals were evident in this sample population. QT_cB was ≥ 420 msec and increased ≥ 10% from baseline at Month 6 for 2 (2.4%) subjects (8502081 and 3543011). For one of these subjects (3543011), other QT_c calculations (ie, QT_cF, QT_cN, and QT_cE) also met the criteria for potential clinical significance; however, the overall interpretation of ECG findings was normal at Month 6 for this subject.

At the last visit, the percentage of subjects who experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline) was 12.7%; whereas, 7.0% of subjects experienced a weight loss of ≥ 7% relative to baseline. There was no signal of increased abdominal obesity associated with aripiprazole and no clinically meaningful changes were observed in z-scores for weight and BMI.

No consistent trends were observed in any of the specific parameters that were evaluated for metabolic abnormalities. However, few subjects reached the Month 12 laboratory evaluation for

fasting glucose, triglycerides, and HDL-C, thus preventing definitive overall conclusions regarding the metabolic syndrome due to the ongoing nature of Study 31-05-243.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Based on a comparison of the results of four adult clinical studies (CN138-007, CN138-008, CN138-009, and CN138-074) in bipolar disorder with the results of this pediatric bipolar disorder study, some AEs (eg, somnolence, blurred vision, and extrapyramidal symptoms) appear to occur at a higher frequency in the pediatric population compared with the adult population with bipolar disorder.

The study design and drug exposure in Study 31-03-240 and 31-03-241 have met agency's PWR requirements. No important limitations of data were detected.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

This submission includes one placebo-controlled efficacy and safety study (31-03-240) which consists of an acute treatment phase and a extension phase, and one long-term open label safety study (31-03-241). Data from each study were not pooled across studies.

7.4.1.2 Combining data

No combing data were reviewed for this submission.

7.4.2 Explorations for Predictive Factors

No further explorations for predictive factors were conducted in these studies.

7.4.3 Causality Determination

Relationship of an adverse event to treatment will be assessed as follows:

Definite: There is a reasonable causal relationship between the study drug and the AE, when the event responds to withdrawal of the study drug (dechallenge), and recurs with rechallenge by administration of the study drug.

Probable: There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge. Rechallenge is not required.

Possible: There is a reasonable causal relationship between the study drug and the AE. Dechallenge is lacking or unclear.

Not Likely: There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the event.

Unrelated: There is not a temporal or causal relationship to the study drug administration.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Study 31-03-240 was a placebo-controlled, fixed-dose study containing 3 arms: the aripiprazole 10 mg, aripiprazole 30 mg, and the placebo arm. Aripiprazole was gradually titrated to 10 mg within 5 days and to 30 mg within 13 days. Patients remained on their target dose for the remainder of the acute treatment phase. All study medications were administered orally.

Study 31-03-241 was a 6-month, flexible-dose, open-label study with a dose range of 2 mg/d to 30 mg/d. Study medications were administered orally on daily basis.

The aripiprazole doses used in these studies are within FDA recommended dose range. There are no specific concerns regarding the study dose regimen.

8.2 Drug-Drug Interactions

The existing label addresses safety outcomes related to potential drug-drug interactions. There have been no new data generated on this topic from this submission.

8.3 Special Populations

This submission contains two completed child/adolescent clinical trials. The effects of aripiprazole on other special populations were not studied in these studies.

8.4 Pediatrics

The efficacy and safety of aripiprazole in the treatment of pediatric bipolar I disorder, manic or mixed episode, with or without psychotic features were demonstrated by the efficacy and safety data from Study 31-03-240. The long-term safety of aripiprazole in the treatment of pediatric schizophrenia and bipolar I disorder (mania and mixed episodes) were demonstrated by the safety data from Study 31-03-241.

The efficacy and safety data from these two studies are comparable to that obtained from adult bipolar clinical trials with the exception of some AEs (eg, somnolence, blurred vision, and extrapyramidal symptoms) appeared to occur at a higher frequency in the pediatric population.

8.5 Advisory Committee Meeting

This submission was not presented to the Psychopharmacology Drug Advisory Committee.

8.6 Literature Review

A worldwide literature search for published articles pertaining to the safety and efficacy of aripiprazole was conducted for NDA 21-436/017 (apripiprazole for schizophrenia indication in adolescents) covering the period from March 1, 2005 through December 1, 2006. The search concluded that the literature contains no findings that would adversely affect conclusions about the safety and efficacy of aripiprazole.

Otsuka submitted an updated literature search, covering the period from December 1, 2006 to June 1, 2007 as an amendment to this NDA on September 27, 2007. The search criteria and databases were same as used for the original NDA filing and all subsequent sNDA filings for aripiprazole, except for the removal of CAS registry numbers as search term and removal of file JICST because the file has been removed from both STN and Dialog. The literature search was conducted by Bristol-Myers Squibb in USA and by Otsuka in Japan and other countries out Japan in Otsuka territory. Following review, it has been determined that the literature contains no findings that would adversely affect conclusions about the safety of aripiprazole contained in supplemental submission to NDA 21-436/S-021.

8.7 Postmarketing Risk Management Plan

There are no additional recommendation regarding post-marketing risk management plan.

8.8 Other Relevant Materials

No other relevant materials were provided during review cycle.

9 OVERALL ASSESSMENT

9.1 Conclusions

Aripiprazole showed efficacy at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared to placebo in the primary efficacy endpoint, mean change in YMRS Total Score at Week 4 (LOCF).

The safety findings from this submission are comparable to that obtained from adult bipolar clinical trials with the exception of some AEs (eg, somnolence, blurred vision, and extrapyramidal symptoms) appeared to occur at a higher frequency in the pediatric population. No any unexpected serious adverse events (SAEs) or deaths associated with aripiprazole treatment were reported.

9.2 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this supplement NDA be granted approvable status.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no further recommendations for risk management activity at this time point.

9.3.2 Required Phase 4 Commitments

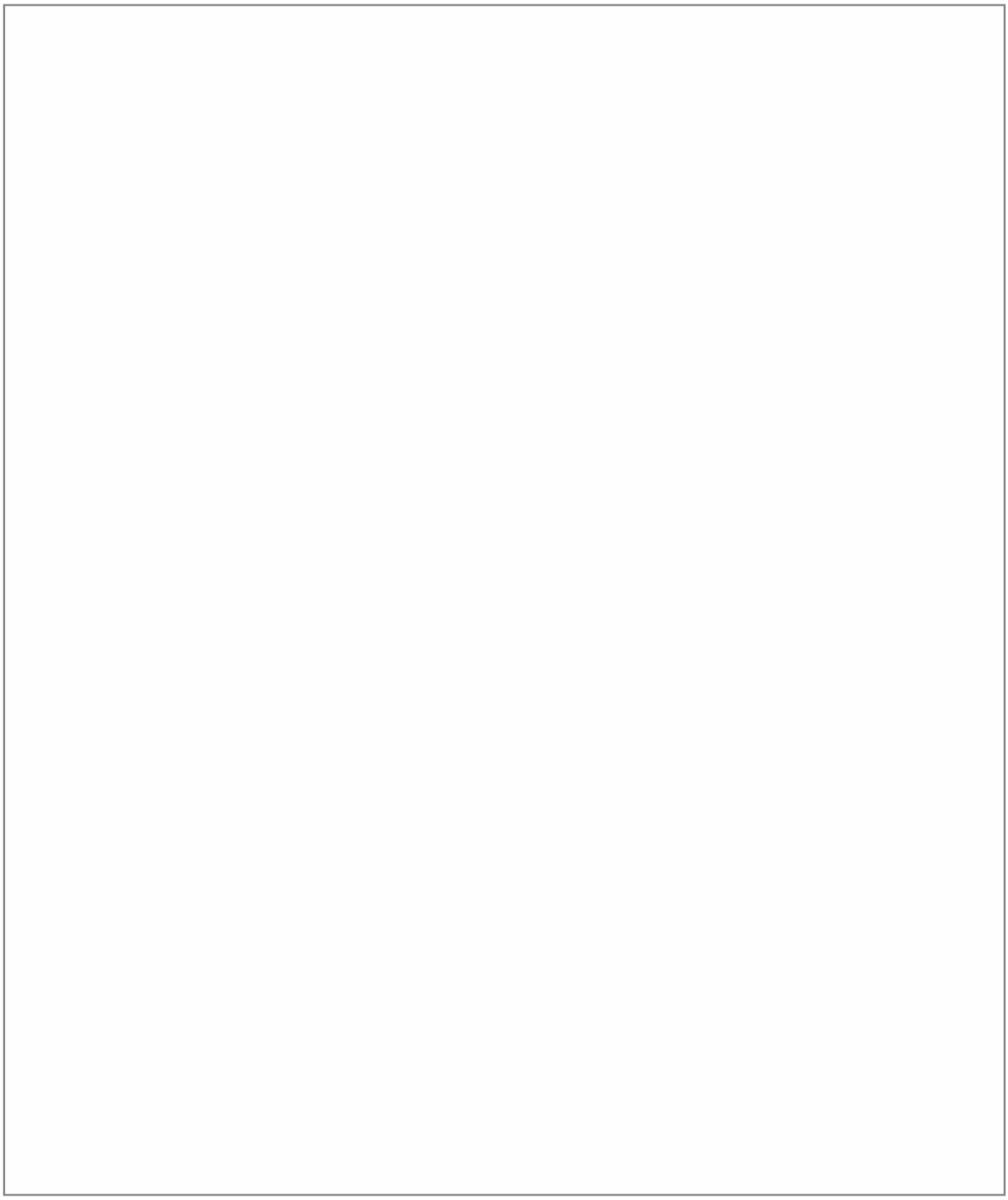
There are no further requirements for phase 4 commitments at this time.

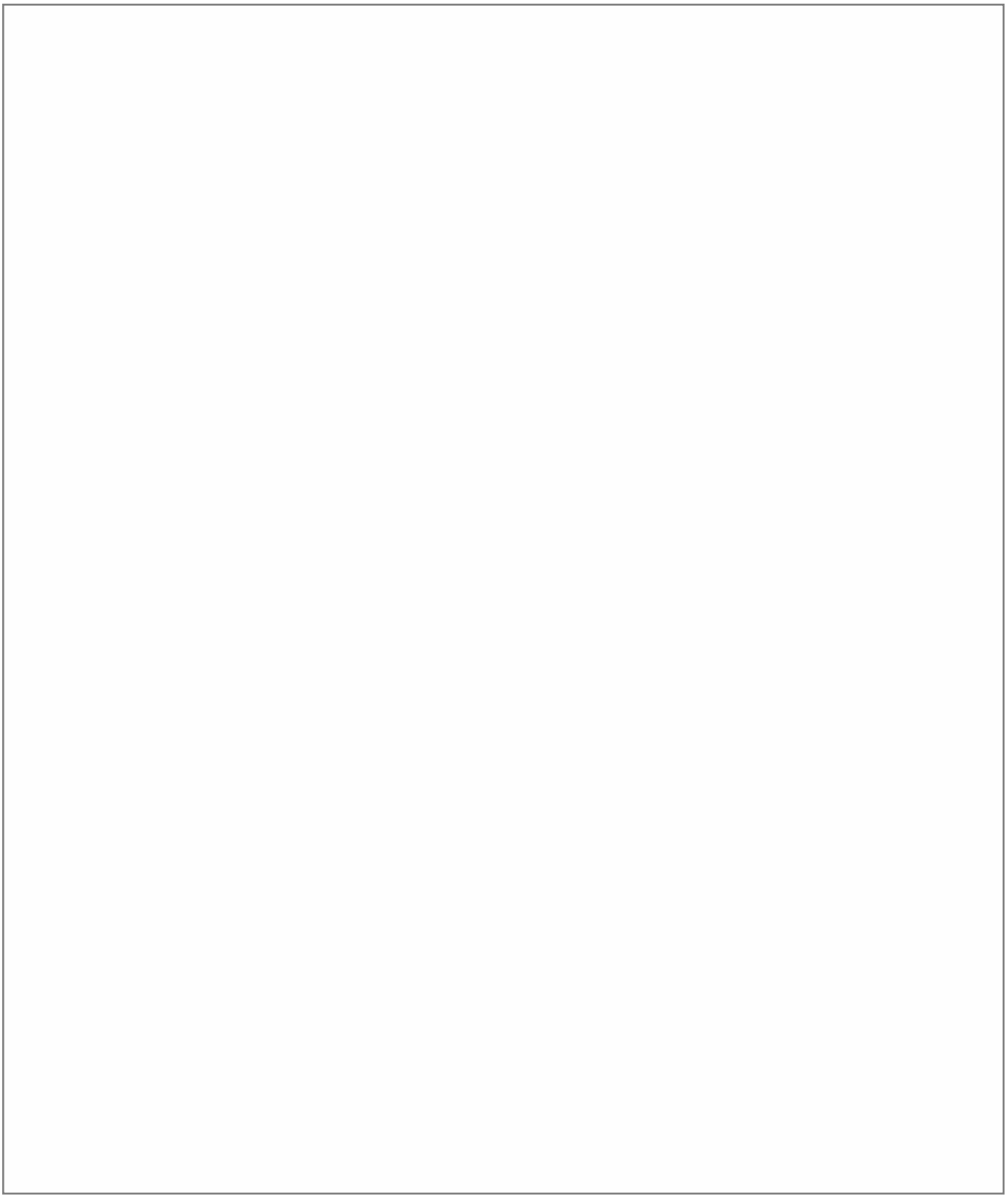
9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

HIGHLIGHTS OF PRESCRIBING INFORMATION





9.5 Comments to Applicant

No additional comments to applicant at this time.

10 APPENDICES

10.1 Investigators and Study Sites in Study 31-03-240

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
002	J. Robert Batterson, MD	Children's Mercy Hospitals and Clinics 2401 Gillham Road Kansas City, MO 64108	3	0
005	Rudy Chavez, MD	Advanced Psychiatric Group 180 North San Gabriel Boulevard Pasadena, CA 91107	0	0
006	Robert L. Findling, MD	University Hospitals of Cleveland Division of Child and Adolescent Psychiatry 11100 Euclid Avenue Cleveland, OH 44106-5080	18	8
007	Carlos Guerra, Jr. MD, PA	Carlos Guerra, Jr. MD, PA 9701 Richmond Avenue Suite 200 Houston, TX 77042	6	5
009	Scott M. Hogan, MD	Pinnacle Pointe Hospital 11501 Financial Centre Parkway Little Rock, AR 72211	7	2
010	Ali A. Kashfi, MD	Ali A. Kashfi, MD 597 Maitland Avenue Altamonte Springs, FL 32701	8	7
011	Alain Katic, MD	Claghorn - Lesem Research Clinic 6750 West Loop South, Suite 1050 Bellaire, TX 77401	6	6
012	Bennett L. Leventhal, MD	Institute for Juvenile Research Department of Psychiatry (M/C 747) University of Illinois at Chicago 1747 W. Roosevelt Road, Room 155 Chicago, IL 60608	2	0

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
013	Adam F. Lowy, MD	Comprehensive NeuroScience, Inc. Psychiatric Institute of Washington 4228 Wisconsin Avenue NW Washington, DC 20016	5	4
016	Marino Molina, Jr. MD CPI	Amedica Research Institute, Inc 625 East 49th Street Hialeah, FL 33013	8	4
019	Syed Jamal Mustafa	Pacific Institute of Medical Sciences 10126 NE 132nd ST Suite C Kirkland, WA 98034	13	9
020	Steven G. Potkin, MD	UC Irvine Medical Center 101 The City Drive South Orange, CA 92868	0	0
021	Sohail Punjwani, MD	Ft. Lauderdale Hospital 1601 E. Las Olas Blvd Ft. Lauderdale, FL 33301	10	9
022	Joachim D. Raese, MD	Behavioral Health 2000, LLC 5945 Brockton Avenue Riverside, CA 92506	4	3
024	Adelaide S. Robb, MD	Children's National Medical Center 111 Michigan Avenue NW Washington DC 20010	9	7
025	Russell E. Scheffer, MD	Children's Health System; Children's Hospital of Wisconsin Child & Adolescent Psychiatry and Behavioral Medicine 9000 West Wisconsin Avenue P.O. Box 1997, MS # 750 Milwaukee, WI 53201-1997	2	1
027	Veronique Sebastian, MD	Sooner Clinical Research 5929 N. May Ave., Suite 401 Oklahoma City, OK 73112	3	2

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
029	Rajinder Shiwach, MD	InSite Clinical Research 1203 Lake Street, Suite 212 Fort Worth, TX 76102	9	8
032	Roger B. Vogelfanger, MD	Research Strategies of Memphis, LLC 668 Colonial Road, Suite 4 Memphis, TN 38117	5	4
033	Kashinath G. Yadalam, MD	Lake Charles Clinical Trials 2770 3rd Ave., Suite 340 Lake Charles, LA 70601	3	2
035	Juan B. Espinosa, MD	Juan B. Espinosa, MD TuKoi Institute for Clinical Research 20820 West Dixie Highway Miami, FL 33180	2	0
037	Robert L. Hendren, DO	M.I.N.D. Institute 2825 50th Street Sacramento, CA 95817	2	1
038	Robert L. Jimenez, MD	Synergy Research, Inc., LLC 1202 E. Sonterra Blvd., Suite 701 San Antonio, TX 78258	9	3
039	Willis Holloway, Jr., MD	Cutting Edge Research Group 6613 N. Meridian Avenue Oklahoma City, OK 73116	6	6
040	Anjali A. Pathak, MD	A.P. Psychiatric & Counseling Services 5251 Emerson Street Jacksonville, FL 32207	4	3
041	Carlos Santana, MD	University of South Florida Department of Psychiatry and Behavioral Medicine 3515 East Fletcher Ave. Tampa, FL 33613	7	4
047	Michael J. Rieser, MD	Michael J. Rieser, MD 2801 Palumbo Drive Suite 202 Lexington, KY 40509	14	10

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
050	Barbara L. Gracious, MD	Department of Psychiatry University of Rochester Medical Center 300 Crittenden Blvd. Rochester, NY 14642	12	2
053	Ismail B. Sendi, MD, MS	New Oakland Child/Adolescent and Family Center 42621 Garfield Rd., Suite #101 Clinton Township, MI 48038	12	9
054	Alan Unis, MD	Sacred Heart Medical Center and Sacred Heart Children's Hospital 101 West 8th Avenue Spokane, WA 99204	10	6
057	Humberto Quintana, MD	Louisiana State University Health Sciences Center School of Medicine, Department of Psychiatry 1542 Tulane Avenue New Orleans, LA 70112	0	0
059	Jean A. Frazier, MD	Cambridge Health Alliance Central Street Health Clinic 26 Central St. Somerville, MA 02143	1	1
060	Naveed Iqbal, MD	Advanced Bio-Behavioral Sciences, Inc. 5 West Main Street Suite 206 Elmsford, NY 10523	3	3
063	Sharon E. Cain, MD	University of Kansas Medical Center 3901 Rainbow Boulevard Kansas City, KS 66160	0	0
064	James McKnight, MD	Mountainview Center For Medical Research 3695 Cascade Road, SW Suite W Atlanta, GA 30331	8	7

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
066	Saul Helfing, MD	Highline-West Seattle Mental Health Center 2600 Southwest Holden Street Seattle, WA 98126	0	0
067	Veena Luthra	Clinical Trial Specialists 1 Belmont Ave, Suite 315 Bala Cynwyd, PA 19004	6	4
068	Ashraf Attalla, MD	Ashraf Attalla, MD 4015 South Cobb Drive, Suite 100 Smyrna, GA 30080	11	9
070	Harinder Grewal, MD	World Wide Research 1908 Sweetwater Road National City, CA 91950	9	7
071	Jeanette Cueva, MD	Bioscience Research, LLC 222 West 14th Street New York, NY 10011	6	6
073	Ann C. Childress, MD	Center for Psychiatry and Behavioral Medicine Inc. 7351 Prairie Falcon Road Suite 160 Las Vegas, NV 89128	1	0
082	John H. Gilliam, MD	International Clinical Research Associates, LLC. 1601 Rolling Hills Drive, Suite 201 Richmond, VA 23229	15	12
901	Grant B. Belnap, MD	Mountain West Clinical Trials 1032 S. Bridgeway Place, Suite 110 Eagle, ID 83616	11	6
902	Joseph Biederman, MD	Massachusetts General Hospital Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD 185 Alewife Brook Parkway Suite 2000 Cambridge, MA 02138	13	10

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
903	Matthew Brams, MD	Bayou City Research, Ltd. 550 Westcott, Suite 310 Houston, TX 77007	10	9
904	Guy E. Brannon, MD	Brentwood Research Institute 1002 Highland Avenue, Suite 400 Shreveport, LA 71101	4	3
905	Gabrielle A. Carlson, MD	SUNY Stony Brook Child & Adolescent Psychiatry Putnam Hall, South Campus Stony Brook, NY 11794-8790	9	6
906	Kiki Chang, MD	Stanford University School of Medicine 401 Quarry Rd Stanford, CA 94305-5719	6	4
907	Deborah Deas, MD, MPH	Institute of Psychiatry 67 President Street 4N-CDAP Charleston, SC 29425	1	0
908	Bradley C. Diner, MD	Arkansas Psychiatric Clinic, PA.. 28 Rahling Circle Little Rock, AR 72223	2	1
909	Timothy R. Smith, MD (08Aug2006 - present) David A. Duesenberg, MD (31 Jan 2005-07 Aug 2006)	Mercy Health Research 12680 Olive Blvd, Ste 200 St. Louis, MO 63141	1	1
910	Michael S. Greenbaum, MD	Capstone Clinical Research 1117 S. Milwaukee Avenue, Suite B-7 Libertyville, IL 60048	3	2
912	Arifulla Khan, MD	Northwest Clinical Research Center 1900-116th Avenue NE Bellevue, WA 98004	19	18

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
913	Michael Plopper, MD	Sharp Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, CA 92123	7	6
916	Elizabeth B. Weller, MD	The Children's Hospital of Philadelphia 3440 Market Street, Suite 200 Philadelphia, PA 19104	0	0
917	Scott Daniel Segal, MD	Scientific Clinical Research, Inc c/o Segal Institute for Clinical Research 1065 N.E. 125th Street, Suite 417 North Miami, FL 33161	8	6
918	David Dunn, MD	Riley Hospital for Children ROC 4300 702 Barnhill Drive Indianapolis, IN 46202-5200	7	7
919	Lawrence D. Ginsberg, MD	Red Oak Psychiatry Associates, PA 17115 Red Oak Dr., Suite 109 Houston, TX 77090	24	18
920	Thomas Gazda, MD	Meadowbrook Research, Inc. 4383 N. 75th Street, Suite 101 Scottsdale, AZ 85251	11	10
921	Keith E. Saylor, PhD	NeuroScience, Inc. 106 Elden Street, Suite 17 Herndon, VA 20170	3	3
923	Birgit H. Amann, MD	Rochester Center for Behavioral Medicine 441 S. Livernois, Suite 205 Rochester Hills, MI 48307	4	1
924	Aradhana (Bela) A. Sood, MD	Virginia Treatment Center for Children Virginia Commonwealth University 515 North 10th Street Richmond, VA 23298	0	0

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
926	Deborah R. Bergen, MD	Cientifica Inc. at Prairie View Inc. 1900 E. First Street Newton, KS 67114	7	5
927	Melissa Delbello, MD	University of Cincinnati Medical Center 231 Albert Sabin Way Cincinnati, OH 45267-0559	2	2
930	David Howard Flaherty, DO	Fidelity Clinical Research, Inc c/o Segal Institute for Clinical Research 7481 W. Oakland Park Blvd, Suite 100 Ft. Lauderdale, FL 33319	3	2
931	Rajinder S. Dhillon, MD	Brighton Research Group, LLC Windwood Centre 780 Lynnhaven Parkway, Suite 285 Virginia Beach, VA 23452	2	2

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/s/

Jing Zhang
2/14/2008 03:09:31 PM
MEDICAL OFFICER

Gwen Zornberg
2/19/2008 11:28:24 PM
MEDICAL OFFICER
I concur with Dr. Zhang's recommendation in her review for an approval action given agancy agreement on labeling with the sponsors for the claim of aripiprazole in the treatment of BP I disorder in pediatric patiients (ages10-17)-