CLINICAL REVIEW

Application Type	NDA 21436-017 NDA 21713-012 NDA 21729-004 NDA 21866-004
Submission Number	017
Submission Code	SE5
Letter Date	March 23, 2007
Stamp Date	March 24, 2007
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Reviewer Name	Jing Zhang, MD, PhD
Review Completion Date	August 22, 2007
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 (b) (4)
Indication	Schizophrenia
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.

I recommend a few labeling changes. Details can be found in section 9.4 Labeling Review.

(b) (4)

Final approval is contingent on mutual agreement on labeling (b) (4)

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 required at this time point.

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.

This submission includes data from 2 completed studies—Study 31-03-238 (PK study) and Study 31-03-239 (acute controlled study for adolescent schizophrenia) and one ongoing study—Study 31-03-241(long-term safety study). From this submission, the sponsor intended to seek for approval of the acute (b) (4) treatment indication for pediatric schizophrenia.

Study 31-03-238 is a child and adolescent PK study designed to assess the safety, tolerability and PK of repeating doses of aripiprazole following oral administration in children (10 to 17 years) with a primary diagnosis of schizophrenia or bipolar disorder. This PK study is reviewed by Andre J. Jackson, PhD, a Bio-Pharm reviewer from OTC/DCRI. At the time of completion of this review, Dr. Jackson's review is still pending.

Study 31-03-239 is a 6-week, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of oral aripiprazole at doses 10 mg/d and 30 mg/d in adolescents (13 to 17 years) with primary diagnosis of schizophrenia. The data from this study including both efficacy and safety data were reviewed in detail in this review.

Study 31-03-241 is an ongoing, 6-month, multicenter, open-label, flexible-dose (2 to 30 mg/d) safety and tolerability study in children and adolescent with primary diagnosis of schizophrenia and bipolar disorder to provide additional long-term safety and tolerability data for oral aripiprazole. The clinical data cut-off date for inclusion of data for this submission was 09 Nov. 2006. The safety data from this study were used to detect deaths and unexpected serious adverse events associated with long-term oral aripiprazole treatment. Aripiprazole's long-term effects on children's growth (waist circumference, BMI, weight, and z-scores) were also reviewed. Because there was no control arm in this study, the value of these data is limited.

The primary components of this supplement NDA are as follows:

- Clinical study report (CSR) for 31-03-238 (PWR required Pharmacokinetic study in the pediatric Schizophrenia and Bipolar Mania population)
- CSR for 31-03-239 (PWR required controlled efficacy and safety study in Adolescent Schizophrenia population)
- Combined Long-term Safety Synopsis for 31-03-239 and the open-label, long-term safety study in pediatric Schizophrenia and Bipolar Mania population, 31-03-241
- Revised Abilify labeling in Physician's Labeling Rule (PLR) format

1.3.2 Efficacy

The efficacy of aripiprazole in the acute schizophrenia treatment in pediatric population was demonstrated by efficacy data from Study 31-03-239. Aripiprazole was effective in the treatment of pediatric schizophrenia at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared to placebo in PANSS total score at Week 6.

1.3.3 Safety

This safety review is based on safety data from Study 31-03-239 and 31-03-241. The safety findings from this submission were consistent with the previously observed aripiprazole safety profile. No any unexpected serious adverse events (SAEs) or deaths associated with aripiprazole treatment were reported.

1.3.4 Dosing Regimen and Administration

Study 31-03-239 is a fixed-dose study. Patients who met the inclusion criteria were randomized into one of following treatment arms: aripiprazole 10 mg, aripiprazole 30 mg or placebo. All study drugs were administered orally for 6 weeks. A one-time dose reduction to 5 mg/day in the 10 mg treatment arm and to 15 mg/day in the 30 mg treatment arm after Day 25 for dose-related tolerability issues was permitted.

Study 31-03-241 is a flexible-dose, open-label study. The dose range was aripiprazole 2 to 30 mg/d administered orally for 6 months.

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 three studies submitted to this submission 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. The safety of aripiprazole tablets has been studied in approximately 8456 adult subjects to date. There is a general lack of clinical research in pediatric and adolescent subjects having schizophrenia.

2.2 Currently Available Treatment for Indications

Risperidone is the only antipsychotic that has been approved by FDA for the indication of pediatric schizophrenia (Aug. 2007). However, other 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 Sates.

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.

April 7, 2004 New protocol for Study 31-03-238 (adolescent PK study) was submitted to FDA.

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

July 1, 2004 New protocol for Study 31-03-239 (adolescent schizophrenia study) was submitted to FDA.

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

Dec. 13, 2006 Otsuka submitted IND 42,776 for the adolescent schizophrenia indication.

Jan. 18, 2007 Pre-NDA meeting with FDA discussed results of adolescent schizophrenia trial done in response to PWR and discussed possible sNDA submission seeking an indication in adolescent population.

Mar. 23, 2007 Otsuka submitted this sNDA for Ability in the treatment of adolescent schizophrenia.

(b) (4)

2.6 Other Relevant Background Information

Abilify (aripiprazole) is approved for the treatment of acute schizophrenia, maintenance of stability in schizophrenia, treatment of acute manic episodes associated with Bipolar I Disorder and for the maintenance of efficacy in Bipolar I Disorder, in the United States. It is also being evaluated for (b) (4) in a collaborative program between Marketing Holder Authorization Otsuka Pharmaceutical Company (OPC) and co-marketer Bristol-Myers Squibb Company (BMS). Besides US, Aripiprazole is marketed for the treatment of schizophrenia in Mexico, Brazil, Puerto Rico, Australia, Korea, Peru, Germany, U.K., Columbia, Chile, Ireland, Switzerland, Sweden, Denmark, Greece, Venezuela, Finland, Iceland, Netherlands and Singapore. Aripiprazole is also approved for the treatment of schizophrenia in Taiwan, Indonesia, France, Spain, Italy, Belgium, Luxembourg, Austria, Hungary, Portugal, Slovakia, Czech Republic, Latvia, Estonia, Poland, Norway, Aruba, Ecuador, Trinidad & Tobago, and Curacao.

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.

3.3 Statistical Review and Evaluation

Yeh-Fong Chen, PhD., is the statistical reviewer for this sNDA. In her review, she confirmed the sponsor's analysis results for the primary and secondary endpoints for Study 31-03-239 and agreed with the conclusion that aripiprazole is effective at doses of 10 mg/d and 30 mg/d in the treatment of pediatric schizophrenia. However, she disagrees with the sponsor's claim that the efficacy results at aripiprazole 30 mg/d were generally stronger than the results at 10 mg/ (b) (4)

(b) (4)

3.4 Bio-Pharmacology Review and Evaluation

Andre J. Jackson, PhD, is the Bio-Pharm reviewer for this submission. At the time of completion of this review, Dr. Jackson's review is still pending.

3.5 Clinical Sites Inspection

Two study sites were selected for inspection by the Division of Scientific Inspection because of relatively larger enrollment in Study 31-03-239. Dr. Michel Woodbury Fariña (Site 074) and Dr. Stefan Todorov (Site 104) are principle investigators in these two sites. The inspections were conducted from Aug. 7, 2007 to Aug. 16, 2007. The inspector found a few minor deficiencies of data at each study site. However, the inspector felt the deficiencies were unlikely to have an effect on data reliability and she concluded that data from these two investigators are acceptable.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Efficacy data to support the efficacy claims in this submission are from Clinical Study Report for Study 31-03-239.

Safety data to support the safety conclusions in pediatric schizophrenia population are from Clinical Study Report for Study 31-03-239 and Combined Long-term Safety Synopsis for 31-03-239 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
31-03-239 A multicenter, randomized, double-blind, placebo controlled and fixed-dose study in treatment of adolescents with primary diagnosis of schizophrenia.	To assess the short-term safety, and efficacy of oral aripiprazole at doses of 10 mg/d and 30 mg/d in adolescents (10 to 17 years).	6 weeks	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
March 23, 2007	Initial sNDA	CSR for Study 31-03-239 Synopsis CSR for combined analysis of Study 31-03-239 and 31-03-241 Case report tablulations (.xpt files) Case report forms
May 22, 2007	Amendment	Additional CRFs A completed literature search for Abilify
June 6, 2007	Amendment	A completed table of information in response to the PWR requirements
June 21, 2007	Amendment	Additional financial disclosure information

(b) (4)

4.4 Data Quality and Integrity

Case Report Forms, Narrative Summaries, and adverse events (.xpt file), as well as AE coding (compared investigator's verbatim terms with MedDRA preferred terms) were examined for consistency of adverse event information across documents and acceptability of AE coding. No significant inconsistency was found.

Two study sites (Site 074 and 104) in Study 31-03-239 were selected for scientific inspection by DSI. Minor deficiencies of data were found at each study site. However, the inspector felt that the deficiencies were unlikely to have an effect on data reliability.

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

As of March 8, 2007 the sponsor received a total of 143 of the 143 financial disclosures for investigators. Two sites had a change in principal investigator during the course of the study, resulting in a total of 143 investigator financial disclosures for 141 sites. One investigator had financial interest information to disclose. The sponsor received 583 of the 593 disclosure forms from sub-investigators. None of the sub-investigators had financial interest information to disclose. There are a total of 10 forms that have not been received to date from sub-investigators.

(b) (6) received $2,500.00 on (b) (6) and he also received $2,500 on (b) (6) Since his site (b) (6) contributed (b) (6) patients to (b) (6) the financial payment (b) (6) received unlikely biased the study results.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Andre J. Jackson, PhD., is the primary Bio-Pharm reviewer. Details can be found in Dr. Jackson's review.

5.2 Pharmacodynamics

Andre J. Jackson, PhD., is the primary Bio-Pharm reviewer. Details can be found in Dr. Jackson's review.

5.3 Exposure-Response Relationships

Exposure-response relationship was not particularly studied in these studies. In Study 31-03-239, aripiprazole 30 mg arm didn't demonstrate significant superiority to aripiprazole 10 mg arm in mean change from baseline in PANSS Total Score (arip 10 mg vs 30 mg: -26.6 vis -28.6).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

In the original submission, Otsuka proposed the acute treatment indication for pediatric schizophrenia. (b) (4)

6.1.1 Methods

The clinical study report for Study 31-03-239 is the main data source for this efficacy review. (b) (4) Data from Study 31-03-241 were mainly reviewed in safety review section. The efficacy review was performed in consultation with the statistical reviewer, Yeh-Fong Chen, PhD.

6.1.2 General Discussion of Endpoints

Positive and Negative Syndrome Scale (PANSS) is the primary endpoint in Study 31-03-239. PANSS is one of most commonly used instruments for measuring symptom reduction of schizophrenia patients in the antipsychotic therapy trials. PANSS is a 30-item rating instrument evaluating the presence/absence and severity of positive, negative and general psychopathology of schizophrenia. Use of the PANSS as a tool for assessing the efficacy of treatments for schizophrenia and other psychotic disorders in studies in pediatric and adolescent patients is well documented. The scale was developed from the Brief Psychiatric Rating Scale (BPRS) and the Psychopathology Rating Scale. All 30 items are rated on a 7-point scale (1=absent, 7=extreme). Compare to BPRS, PANSS addresses broader psychopathology and has greater reliability. However, challenges of the PANSS are difficulties to conduct patient interview (30-40 min.) and patient subjectiveness (items are assessed based on patient perceptions).

Primary Endpoint:
Mean change from baseline to endpoint in the PANSS total score

Secondary Endpoint:

- Mean change from baseline to endpoint in the children's Global Assessment Scale (CGAS)
- Mean change from baseline to endpoint in the Clinical Global Impression Severity (CGI-S) Scale and CGI-Improvement Scale
- Mean change from baseline to endpoint in the PANSS Positive and Negative Subscales
- Time to discontinuation due to all reasons

6.1.3 Study Design

6.1.3.1 Investigators/Sites

Study 31-03-239 was conducted in Argentina, Bulgaria, Croatia, India, Jamaica, Mexico, Romania, Russia, Serbia, South Africa, South Korea, Ukraine, and the US in approximately 300 subjects at 141 study centers. The principal investigators, study centers, and number of subjects screened and enrolled per center are listed in Appendices 10.1.

6.1.3.2 Objectives

The primary objective of the study is to determine the safety and efficacy of aripiprazole tablets at doses of 10 mg/day and 30 mg/day in adolescent patients, ages 13-17 years, with primary diagnosis of schizophrenia.

6.1.3.3 Subjects

Key Inclusion Criteria:

- Male and Female patients aged 13 to 17 with a K-SADS-PL confirmed DSM-IV diagnosis of schizophrenia. Schizophrenia must be the primary DSM-IV axis I diagnosis.
- Patients who have a PANSS score ≥ 70 at baseline.

Exclusion Criteria:

- Patients with an Axis I diagnosis of schizoaffective disorder, or a current diagnosis of major depressive episode.
- Patients presenting with a clinical picture and/or history that is consistent with delirium, amnestic or other cognitive disorder, or bipolar disorder; Subjects with psychotic symptoms that are better accounted for by another general medical condition or direct psychological effect of a substance (i.e., medication).
- Patients hospitalized within 14 days prior to screening visit for current acute episode of schizophrenia.
- Patients with known mental retardation.
- Patients with childbearing potential, who are not practicing double-barrier birth control, or, who will not remain abstinent during the study, and for 30 days (for females) and for 90 days (for males) following the last dose of study medication.
- Females who are breast-feeding and/or who have a positive urine and/or serum pregnancy test result, prior to receiving study drug.
- The patient had been previously involved in a clinical study with aripiprazole or is currently treated with aripiprazole.
- The patient has a known allergy or hypersensitivity to aripiprazole or other quinolinones.
- The patient is considered treatment resistant to antipsychotic medication, in the opinion of the investigator, based on prior trials of two different antipsychotics that were of adequate dose and duration.
- The patient has a history of neuroleptic malignant syndrome.
- The patient represents a significant risk of committing suicide, or with a score > 3 on the Suicidal Ideation item of the Children's Depression Rating Scale-Revised (CDRS-R).
- The patient has met DSM-IV criteria for substance or alcohol abuse or dependence within the past 3 months with the exception of abuse of marijuana.
- A positive drug screen for substance use (excluding marijuana).
- The patients have clinically significant medical conditions.
- The patient has participated in any clinical trial with an investigational product within the past month.

6.1.3.4 Overall Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study designed to assess the safety and efficacy of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in adolescent patients, ages 13 to 17 years, with a DSM-IV diagnosis of schizophrenia.

The study consists of three arms. After a minimum of a 3-day antipsychotic washout period, subjects were randomized to either 10 mg or 30 mg of aripiprazole, or to placebo. All study medications were administered orally. Aripiprazole was titrated to the target dose in 5 days in the

10 mg treatment arm, and in 11 days in the 30 mg treatment arm. Patients remained at the assigned fixed dose for at least two weeks. Patients who experienced dose-related tolerability issue prior to study Day 25, were discontinued from the study. After study Day 25, investigators were able to decrease the dose of aripiprazole for tolerability to 5 mg/day in the 10 mg treatment arm and to 15 mg/day in the 30 mg treatment arm.

This 42 days (6-week) study was conducted either on an outpatient basis or in a partial or full inpatient basis at any given time of the study. Mandatory patient evaluations took place at Days 1 (Baseline), (phone call on Day 4), 7, 14, 21, 28, 35, and 42. Eligible patients who completed the 42-day study had the option to enroll into an open-label safety trial of aripiprazole (protocol number: 31-03-241) for an additional six months.

Any mood-stabilizing medications, antidepressants, or psychotropics must have been discontinued at least 3 days (fluoxetine for 4 weeks) prior to administration of study drug (or placebo). Stimulants or other ADHD medications (e.g., atomoxetine) must have been discontinued for 5 halflives prior to receiving the first dose of study drug (or placebo).

During the course of study, if the primary efficacy endpoint is unchanged or worsened, or if deemed absolutely necessary by the treating physician, patients might 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.

6.1.3.5 Statistical Analysis Plan

The core dataset for all efficacy analyses is the Intent-to-Treat (ITT) dataset which consist of data from all randomized subjects. In order to assess sensitivity of results due to missing data, two types of analyses—the LOCF and the OC are performed at a given visit. In order to understand time trends in efficacy, both the LOCF and AC analyses are performed at each visit.

Demographic characteristics, disease severity and medical history at (pre-dose) baseline were summarized by descriptive statistics, e.g., proportion, mean, median, standard deviation, minimum and maximum values. These summary statistics were reviewed to identify any potential lack of balance between the treatment groups.

The primary efficacy variable in this study is the change from baseline in PANSS Total Score. The primary statistical comparisons of interest are (a) aripiprazole 10 mg target dose vs. placebo, and (b) aripiprazole 30 mg target dose vs. placebo. Statistical analysis are performed by fitting an Analysis of Covariance (ANCOVA) model to the PANSS change scores with right hand terms for treatment, regional strata, and baseline total score. The Least Squares Means (LSM) obtained from a type III analysis using SAS are used to estimate the treatment comparisons. A nominal overall significance level of 0.05 (two-tailed) is used in testing statistical significance of these two comparisons. However, in order to account for multiplicity in testing the two comparisons, the Hochberg's procedure is used. In particular, the following procedure is followed. If both p-values are less than 0.05 (two-tailed), then statistical significance is declared for both doses;

however, if the larger of the two p-values is greater than 0.05 then the smaller p-value would be compared with 0.025 (two-tailed) and the corresponding treatment comparison will be declared statistically significant if this p-value is less than 0.025.

6.1.4 Efficacy Findings

6.1.4.1 Subject Disposition

Overall subject disposition is summarized in Table 3. A total of 302 subjects were randomized and treated in this study: 100/302 (33.1%) in the aripiprazole 10 mg arm, 102/302 (33.8%) in the aripiprazole 30 mg arm, and 100/302 (33.1%) in the placebo arm. Of these, 93/302 (30.8%) were randomized in the US, 141/302 (46.7%) were randomized in Europe, and 68/302 (22.5%) were randomized in other regions. All randomized subjects were included in the efficacy and safety analyses.

Subjects who completed the Day 42 visit were defined as completers. A total of 258/302 (85.4%) subjects completed the study: 84/100 (84.0%) in the aripiprazole 10 mg arm, 84/102 (82.4%) in the aripiprazole 30 mg arm, and 90/100 (90.0%) in the placebo arm.

Overall, adverse events (AEs) and subject withdrawal of consent were the most common reasons for discontinuation. A total of 7/100 (7.0%), 4/102 (3.9%), and 2/100 (2.0%) subjects withdrew due to AEs in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively.

Table 3 Subject Disposition

	Aripiprazole 10 mg N (%)	Aripiprazole 30 mg N (%)	Placebo N (%)	Total N (%)
Randomized	100 (100.0)	102 (100.0)	100 (100.0)	302 (100.0)
Completed	84 (84.0)	84 (82.4)	90 (90.0)	258 (85.4)
Discontinued	16 (16.0)	18 (17.6)	10 (10.0)	44 (14.6)
AEs	7 (7.0)	4 (3.9)	2 (2.0)	13 (4.3)
Lost to follow up	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Subject withdrew consent	4 (4.0)	12 (11.8)	5 (5.0)	21 (7.0)
Protocol deviation	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.7)
Lack of efficacy*	5 (5.0)	1 (1.0)	1 (1.0)	7 (2.3)
Analyzed for safety[a]	100 (100.0)	102 (100.0)	100 (100.0)	302 (100.0)
Analyzed for efficacy[b]	100 (100.0)	102 (100.0)	100 (100.0)	302 (100.0)

*: Lack of efficacy was determined by the investigators.
a: Subjects who received at least one dose of study medication were included in the safety analyses.
b: Randomized subjects evaluated for at least one primary or secondary efficacy parameter were included in the efficacy analysis.

A summary of subject disposition by regions is provided in Table 4. The overall completion and discontinuation rate cross regions was similar. Europe had slightly higher completion rate (89.4%) compared to US (81.7%) or Other Region (82.4%), which is caused by very low discontinuation rate in placebo arm in Europe (0% vs. 19.4% in US and 18.2% in Other Region).

Table 4 Subject Disposition by Regions

	Aripiprazole 10 mg N (%)	Aripiprazole 30 mg N (%)	Placebo N (%)	Total N (%)
Randomized	100 (100.0)	102 (100.0)	100 (100.0)	302 (100.0)
US	31 (100.0)	31 (100.0)	31 (100.0)	93 (100.0)
Europe	47 ((100.0)	47 (100.0)	47 (100.0)	141 (100.0)
Other region	22 (100.0)	24 (100.0)	22 (100.0)	68 (100.0)
Completed	84 (84.0)	84 (82.4)	90 (90.0)	258 (85.4)
US	26 (83.9)	25 (80.6)	25 (80.6)	76 (81.7)
Europe	39 (83.0)	40 (85.1)	47 (100.0)	126 (89.4)
Other region	19 (86.4)	19 (79.2)	18 (81.8)	56 (82.4)
Discontinued	16 (16.0)	18 (17.6)	10 (10.0)	44 (14.6)
US	5 (16.1)	6 (19.4)	6 (19.4)	17 (18.3)
Europe	8 (17.0)	7 (14.9)	0 (0.0)	15 (10.6)
Other region	3 (13.6)	5 (20.8)	4 (18.2)	12 (17.6)

6.1.4.2 Demographic Characteristics

Demographic characteristics are summarized in Table 5. The three treatment arms were demographically similar. The majority of subjects were male (171/302, 56.6%), and Caucasian (180/302, 60.0%). The mean age was 15.5 years. Male and Caucasian population were slightly lower respectively in Aripiprazole 10 mg arm (45%, 54%) compare to Aripiprazole 30 mg (63.7%, 64.0%) or placebo (61%, 60%) arm. Black population was slightly higher (17%) in Aripiprazole 10 mg compare to Aripiprazole 30 mg (11%) or Placebo (6%).

Table 5 Demographic Characteristics - All Randomized Subjects

Characteristic		Aripiprazole 10 mg (N = 100)	Aripiprazole 30 mg (N = 102)	Placebo (N = 100)	Total (N = 302)
Age (years)	N	100	102	100	302
	Mean (SD)	15.6 (1.3)	15.4 (1.4)	15.4 (1.4)	15.5 (1.4)
BMI	N	100	102	100	302
	Mean (SD)	23.5 (6.0)	23.0 (4.9)	22.9 (5.3)	23.1 (5.4)
Gender	Male, n (%)	45 (45.0)	65 (63.7)	61 (61.0)	171 (56.6)
	Female, n (%)	55 (55.0)	37 (36.3)	39 (39.0)	131 (43.4)
Race	Caucasian, n (%)	54 (54.0)	62 (61.0)	64 (64.0)	180 (60.0)
	Black, n (%)	17 (17.0)	11 (11.0)	6 (6.0)	34 (11.0)
	Asian, n (%)	16 (16.0)	12 (12.0)	15 (15.0)	43 (14.0)
	Others, n (%)	13 (13.0)	17 (17.0)	15 (15.0)	45 (14.6)

6.1.4.3 Disease Characteristics

Baseline disease severity, as measured by PANSS Total Score, CDRS-R Suicidal Ideations Score, and treatment status for previous episodes, are presented in Table 6. Overall, the baseline disease severity was comparable across all treatment arms. The mean PANSS Total Score and

CDRS-R Suicidal Ideations Score was 94.1 and 1.3, respectively. A total of 223/302 (74.0%) subjects had received treatment for previous episodes.

Table 6 Baseline Disease Severity

Characteristic		Aripiprazole 10 mg (N = 100)	Aripiprazole 30 mg (N = 102)	Placebo (N = 100)	Total (N = 302)
PANSS Total Score	N Mean (SD)	100 93.6 (15.7)	102 94.0 (16.1)	100 94.6 (15.6)	302 94.1 (15.8)
CDRD-R Suicidal Ideation Score	N Mean (SD)	100 1.3 (0.6)	102 1.3 (0.6)	99 1.3 (0.5)	301 1.3 (0.6)
Treatment given for previous episodes	Yes, n (%)	75 (75.0)	75 (74.0)	73 (73.0)	223 (74.0)

6.1.4.4 Concomitant Medications

Concomitant medications received by the subjects during study therapy (≥ 3% incidence overall) are presented in Table 7. The most commonly used medications during the follow-up period (by ≥ 3% incidence overall) were trihexyphenidyl and lorazepam. The psycholeptic utilization rate was very similar cross all treatment arms. It is less likely that concomitant medication use in this study would affect the efficacy outcomes.

Table 7 Concomitant Medications Used Most Commonly (≥ 3%) During Study Treatment

Drug Class/Medication Generic Name[a]	**Aripiprazole 10 mg (N = 100) n (%)[b]**	**Aripiprazole 30 mg (N = 102) n (%)[b]**	**Placebo (N = 100) n (%)[b]**	**Total (N = 302) n (%)[b]**
Total Using One or More Medications	55 (55.0)	59 (57.8)	47 (47.0)	161 (53.3)
Analgesics				
cotylenol	3 (3.0)	3 (2.9)	3 (3.0)	9 (3.0)
paracetamol	4 (4.0)	5 (4.9)	1 (1.0)	10 (3.3)
Anti-Parkinson Drugs				
benzatropine mesilate	3 (3.0)	5 (4.9)	1 (1.0)	9 (3.0)
biperiden	2 (2.0)	7 (6.9)	0 (0.0)	9 (3.0)
trihexyphenidyl	7 (7.0)	11 (10.8)	1 (1.0)	19 (6.3)
Anti-inflammatory and antirheumatic products				
ibuprofen	2 (2.0)	4 (3.9)	3 (3.0)	9 (3.0)
Psycholeptics				
clonazepam	3 (3.0)	4 (3.9)	3 (3.0)	10 (3.3)
diazepam	6 (6.0)	1 (1.0)	3 (3.0)	10 (3.3)
lorazepam	21 (21.0)	22 (21.6)	19 (19.0)	62 (20.5)
Vitamins	3 (3.0)	4 (3.9)	2 (2.0)	9 (3.0)

6.1.4.5 Efficacy Results

6.1.4.5.1 Primary Variable

The mean change from baseline to end point (6 weeks) in PANSS Total Score

The mean changes from baseline to end point in PANSS Total Score for the 10 mg and 30 mg aripiprazole arms versus placebo are presented in Table 8. Aripiprazole 10 mg and 30 mg showed statistically significant improvements over placebo in the PANSS Total Score at Week 6. Using the LOCF data set, the PANSS Total Scores at Week 6 were −26.7 in the aripiprazole 10 mg arm, −28.6 in the aripiprazole 30 mg arm, and −21.2 in the placebo arm. The comparison between aripiprazole and placebo was significant at both doses (p = 0.0414 for arip 10 mg vs placebo; p = 0.0061 for arip 30 mg vs placebo). The difference from placebo in mean change from baseline at Week 6 was −5.46 (95% CI = −10.7 to -0.21; p = 0.0414) for the aripiprazole 10 mg arm and −7.40 (95% CI = −12.7 to −2.13; p = 0.0061) for the aripiprazole 30 mg arm using LOCF dataset.

Table 8 Mean Change from Baseline to Endpoint in PANSS Total Score (LOCF)

	Aripiprazole 10 mg N = 99	Aripiprazole 30 mg N = 97	Placebo N = 98	P – value Aripiprazole vs Placebo	
				10 mg	30 mg
Baseline (LS Mean)	93.7	94.9	95.0		
Mean Change (LS Mean)	-26.7	-28.6	-21.2	0.0414	0.0061

The mean change from baseline in PANSS Total Score (LOCF) by visit is presented in Table 9. The aripiprazole 10 mg arm showed improvements over the placebo arm in the change from baseline in PANSS Total Score at all visits; however, the improvements were only statistically significant compared with placebo at Week 6. The aripiprazole 30 mg arm showed statistically significant improvements over placebo at Week 1, 3, 4, 5 and 6.

Table 9 Mean Change from Baseline to Endpoint in PANSS Total Score by Week (LOCF)

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]	99	93.7	97	94.9	98	95.0	0.5375	0.9372
Week 1	98	-6.9	95	-10.4	97	-7.2	0.8390	0.0465
Week 2	99	-13.9	97	-15.2	98	-12.5	0.4748	0.1828
Week 3	99	-18.4	97	-22.1	98	-16.7	0.4759	0.0269
Week 4	99	-21.8	97	-24.6	98	-19.0	0.2346	0.0181
Week 5	99	-24.5	97	-27.3	98	-20.3	0.0979	0.0057
Week 6[d]	99	-26.7	97	-28.6	98	-21.2	0.0414	0.0061

a: The LS means were the adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata. A negative LS mean indicates 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. Maximum positive score = 210.
d: Primary endpoint.

Using the OC dataset, the PANSS Total Scores at Week 6 were −30.6 in the aripiprazole 10 mg arm, −31.9 in the aripiprazole 30 mg arm, and −22.3 in the placebo arm. The comparison between aripiprazole and placebo was significant at both doses (p = 0.0011 for arip 10 mg vs placebo; p = 0.0002 for arip 30 mg vs placebo). The difference from placebo in mean change from baseline at Week 6 was -8.3.1 (95% CI = -13.3 to -3.37; p = 0.0011) for the aripiprazole 10 mg arm and -9.64 (95% CI = −14.6 to −4.71; p = 0.0002) for the aripiprazole 30 mg arm using OC dataset (see Table 26 in Appendices 10.2).

6.1.4.5.2 Secondary Variables

All secondary variables in this study are non-key secondary variables.

Change from baseline in Children's Global Assessment Scale (CGAS) Score
The CGAS is a measure to provide a global measure of level of functioning in children and adolescents. The measure provides a single global rating only, on scale of 1-100. The mean change from baseline in CGAS Score at Week 6 (LOCF) is presented in Table 10. 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 Week 6 using the LOCF and OC data sets. At Week 6, the mean changes from baseline using LOCF were 14.7, 14.8, and 9.8 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively (p = 0.0054 for 10 mg vs placebo and p = 0.0044 for 30 mg vs placebo).

Table 10 Mean Change from Baseline to Endpoint in CGAS Score (LOCF)

	Aripiprazole 10 mg N = 97	Aripiprazole 30 mg N = 94	Placebo N = 98	P – value Aripiprazole vs Placebo	
				10 mg	30 mg
Baseline (LS Mean)	46.7	45.6	45.4		
Week 6 (LS Mean)	14.7	14.8	9.8	0.0054	0.0044

Change from Baseline in Clinical Global Impression (CGI) Severity Score
The CGI is one of the most widely used brief assessment tools in psychiatry. This is a three-item scale to measure overall illness severity. The mean change from baseline in the CGI-Severity Score (LOCF) is presented in Table 11. The difference from placebo in mean change from baseline at Week 6 for the aripiprazole 10 mg arm was −0.36 (95% CI = −0.62 to −0.10; p = 0.0071) and for the aripiprazole 30 mg arm was −0.42 (95% CI = −0.68 to −0.16; p = 0.0016). The OC analysis results were consistent with that using LOCF analysis.

Table 11 Mean Change from Baseline to Endpoint in CGI Severity Score (LOCF)

	Aripiprazole 10 mg N = 99	Aripiprazole 30 mg N = 97	Placebo N = 98	P – value Aripiprazole vs Placebo	
				10 mg	30 mg
Baseline (LS Mean)	4.5	4.6	4.6		
Week 6 (LS Mean)	-1.2	-1.3	-0.9	0.0054	0.0044

Change from baseline in PANSS Positive Subscale Score
Improvements over placebo in the mean change from baseline in PANSS Positive Subscale Scores were observed for both the aripiprazole 10 mg and 30 mg arms at all time points using the LOCF and OC data sets.

Using LOCF data set, the difference from placebo in mean change from baseline at Week 6 was −1.95 (95% CI = −3.49 to −0.41; p = 0.0134) for the aripiprazole 10 mg arm and −2.47 (95% CI = −4.02 to −0.92; p = 0.0018) for the aripiprazole 30 mg arm. The OC analysis results were consistent with the findings observed from LOCF analysis. Table 12 shows the mean changes from baseline in the PANSS Positive Subscale Score using the LOCF dataset.

Table 12 Mean Change from Baseline to Endpoint in PANSS Positive Subscale Score (LOCF)

	Aripiprazole 10 mg N = 99	Aripiprazole 30 mg N = 97	Placebo N = 98	P – value Aripiprazole vs Placebo	
				10 mg	30 mg
Baseline (LS Mean)	22.1	23.5	22.9		
Week 6 (LS Mean)	-7.6	-8.1	-5.6	0.0134	0.0018

6.1.4.5.3 Subgroup Analyses

Subgroup analyses were performed to evaluate the mean change from baseline to endpoint in PANSS total score for region, gender, and race for Study 31-03-239. Since this study was an adolescent study (13 to 17 years), no age subgroup analysis was performed. Except the comparisons between aripiprazole 30 mg and placebo for male and for white patients, all other comparisons had nominal p-values >0.05. Since these subgroup analyses are only for the exploratory purpose, the p-values should be interpreted with caution.

6.1.5 Clinical microbiology

Clinical microbiology was not studied in this study and the study was not deemed as necessary.

6.1.6 Efficacy Conclusions

Aripiprazole was effective in the acute treatment of adolescent subjects with schizophrenia at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared with placebo in PANSS Total Score at Week 6 (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. This approach is also explicated in the FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Product (Part II, C.2.c). In our PWR on Feb. 11, 2003, we required "a single, independent, adequate and well-controlled clinical trial in adolescent schizophrenia"

"to permit a pediatric claim for a drug already approved in adults". Therefore, the efficacy data from Study 31-03-239 are felt to provide sufficient evidence to support the indication of aripiprazole for the acute schizophrenia treatment in adolescents.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The integrated safety review for this submission is mainly based on safety data from Study 31-03-239, a placebo-controlled, 6-week study. In addition, the safety data from study 31-03-241, an open-label, 6 months safety and tolerability study are also reviewed to assess long-term safety and tolerability of oral aripiprazole and to detect any deaths, and unexpected, serious adverse events. The databases 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 well established, 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 same as its current labeling.

7.1.1 Deaths

No deaths were reported in Study 31-03-239. One death occurred during Study 31-03-241. Subject 8552084 was accidentally electrocuted after receiving approximately 20 weeks of aripiprazole. This event was considered to be unrelated to treatment.

7.1.2 Other Serious Adverse Events

A total of 8/202 (4.0%) aripiprazole treated subjects and 3/100 (3.0%) placebo-treated subjects experienced SAEs in Study 31-03-239, the majority of which were severe in intensity.

The most commonly reported SAEs overall were psychotic disorder (1 subject in each treatment arm) and schizophrenia (1 subject in each aripiprazole treatment arm). The following SAEs were reported by 1 subject each in the aripiprazole 10 mg arm: extrapyramidal disorder, possible neuroleptic malignant syndrome, aggression, psychotic disorder, schizophrenia, and thrombophlebitis. In the aripiprazole 30 mg arm, the following SAEs were reported by 1 subject each: varicella, depression, psychotic disorder, schizophrenia, and suicidal ideation. In the placebo arm, intentional overdose, overdose, psychotic disorder, and suicide attempt were reported by 1 subject in each SAE. Table 13 presents all SAEs reported in the study.

Table 13 All Serious Treatment-emergent Adverse Events

Class and MedDRA Preferred Term	Aripiprazole 10 mg (N = 100) n (%)	Aripiprazole 30 mg (N = 102) n (%)	Placebo (N = 100) n (%)	Total (N = 302) n (%)
Total subjects with at least one SAE	4 (4.0)	4 (3.9)	3 (3.0)	11 (3.6)
Infections and Infestations				
Varicella	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Injury, Poisoning, and Procedural Complications				
Intentional overdose	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Overdose	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Nervous System Disorders				
Extrapyramidal disorder	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Neuroleptic malignant syndrome [a]	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychiatric Disorders				
Aggression	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Depression	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Psychotic disorder	1 (1.0)	1 (1.0)	1 (1.0)	3 (1.0)
Schizophrenia	1 (1.0)	1 (1.0)	0 (0.0)	2 (0.7)
Suicidal ideation	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Suicide attempt	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Vascular Disorders				
Thrombophlebitis	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)

In Study 31-03-241 (long term safety study), 22 (7.8%) subjects experienced SAEs during the study. The pattern of SAEs matches that observed in Study 31-03-239. Worsening or exacerbation of schizophrenia (2.1%) was the most common SAE, followed by psychotic disorder (1.4%), aggression (0.7%), and suicidal ideation (0.7%). No unexpected SAEs were observed.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of Dropouts

Overall profile of dropouts is summarized in Table 14. The overall discontinuation rate was 14.6%. AEs and subject withdrawal of consent were the most common reasons for discontinuation. A total of 7/100 (7.0%), 4/102 (3.9%), and 2/100 (2.0%) subjects withdrew due to AEs and 4/100 (4.0%), 12/102 (11.8%), and 5/100 (5.0%) subjects withdrew consent in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively. Additionally, 5/100 (5.0%) subjects withdrew due to lack of efficacy in the aripiprazole 10 mg arm as determined by the investigator, compared with 1/102 (1.0%) in the aripiprazole 30 mg arm and 1/100 (1.0%) in the placebo arm.

Table 14 Subject Discontinuation

	Aripiprazole 10 mg N=100	Aripiprazole 30 mg N=102	Placebo N=100	Total N=302
Discontinued N (%)	16 (16.0)	18 (17.6)	10 (10.0)	44 (14.6)
Adverse event	7 (7.0)	4 (3.9)	2 (2.0)	13 (4.3)
Lost to follow up	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Subject withdrew consent	4 (4.0)	12 (11.8)	5 (5.0)	21 (7.0)
Protocol deviation	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.7)
Lack of efficacy	5 (5.0)	1 (1.0)	1 (1.0)	7 (2.3)

7.1.3.2 Adverse events associated with dropouts

Table 15 presents all TEAEs resulting in discontinuation of study medication. A total of 13/302 (4.3%) subjects discontinued study medication due to a TEAE: 7/100 (7.0%) in the aripiprazole 10 mg arm, 4/102 (3.9%) in the aripiprazole 30 mg arm, and 2/100 (2.0%) in the placebo arm. Aripiprazole 10 mg arm was associated with higher discontinuation rate due to AEs. The majority AEs were moderate to severe in intensity.

The most commonly reported TEAEs resulting in discontinuation of study medication were psychotic disorder and schizophrenia. Other TEAEs resulting in discontinuation of study medication were: dystonia, somnolence, anxiety, and hypomania in the aripiprazole 10 mg arm; nausea and varicella in the aripiprazole 30 mg arm; and overdose in the placebo arm.

Table 15 TEAEs Resulting in Discontinuation of Study Medication

Class and MedDRA Preferred Term	**Aripiprazole 10 mg (N = 100) n (%)**	**Aripiprazole 30 mg (N = 102) n (%)**	**Placebo (N = 100) n (%)**	**Total (N = 302) n (%)**
Total subjects who discontinued due to AE	7 (7.0)	4 (3.9)	2 (2.0)	13 (4.3)
Gastrointestinal Disorders				
Nausea	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Infections and Infestations				
Varicella	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Injury, Poisoning, and Procedural Complications				
Overdose	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Nervous System Disorders				
Dystonia	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Somnolence	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychiatric Disorders				
Anxiety	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hypomania	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychotic disorder	1 (1.0)	1 (1.0)	1 (1.0)	3 (1.0)
Schizophrenia	2 (2.0)	1 (1.0)	0 (0.0)	3 (1.0)

7.1.3.3 Other significant adverse events

TEAEs associated with EPS-related symptoms are listed in Table 16. The most commonly reported TEAEs associated with EPS-related symptoms (≥ 5% incidence in any treatment group) were akathisia (5.0% in the aripiprazole 10 mg, 11.8% in the aripiprazole 30 mg, and 5.0% in the placebo); extrapyramidal disorder (13.0% in the aripiprazole 10 mg, 21.6% in the aripiprazole 30 mg arm, and 5.0% in the placebo); and tremor (2.0% in the aripiprazole 10 mg, 11.8% in the aripiprazole 30 mg arm, and 2.0% in the placebo). The incidence of these TEAEs, as well as that for salivary hypersecretion, gait disturbance, drooling, dyskinesia, and myoclonus increased with dose of aripiprazole. The majority of EPS related events were mild or moderate in severity and only one event (dystonia, 30 mg arm) led to discontinuation from the study.

Table 16 TEAEs Associated with EPS Symptoms

Class and MedDRA Preferred Term	Aripiprazole 10 mg (N = 100) n (%)	Aripiprazole 30 mg (N = 102) n (%)	Placebo (N = 100) n (%)	Total (N = 302) n (%)
Gastrointestinal Disorders				
Salivary hypersecretion	1 (1.0)	3 (2.9)	1 (1.0)	5 (1.7)
General Disorders and Administration Site Conditions				
Gait disturbance	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Musculoskeletal and Connective Tissue Disorders				
Joint stiffness	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Muscle rigidity	1 (1.0)	1 (1.0)	0 (0.0)	2 (0.7)
Nervous System Disorders				
Akathisia	5 (5.0)	12 (11.8)	5 (5.0)	22 (7.3)
Drooling	0 (0.0)	3 (2.9)	0 (0.0)	3 (1.0)
Dyskinesia	1 (1.0)	2 (2.0)	0 (0.0)	3 (1.0)
Dystonia	3 (3.0)	1 (1.0)	0 (0.0)	4 (1.3)
Extrapyramidal disorder	13 (13.0)	22 (21.6)	5 (5.0)	40 (13.2)
Hyperkinesia	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Myoclonus	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Neuroleptic malignant syndrome[a]	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Tremor	2 (2.0)	12 (11.8)	2 (2.0)	16 (5.3)

Compared with adult population, there were more EPS-related symptoms reported in this study. For aripiprazole treatment, the incidence of EPS-related events (excluding akathisia) in adults ranged from 13 to 15% in short-term trials of schizophrenia and bipolar mania compared to 25% in Study 31-03-239. For akathisia-related events, the incidence in adults ranged from 8 to 15% versus 9% in adolescents.

7.1.4 Other Search Strategies

No other search strategies were warranted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were assessed at all visits. In addition, the site called the subject on Day 4, between the visits on Day 1 and Day 7, to assess adverse events during the forced titration period. In order to avoid bias in eliciting adverse events, subjects were asked non-leading question, such as, "How are you feeling?" All adverse events reported by the subject must be recorded on the source documents and case report forms provided by the Sponsor.

7.1.5.2 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.

7.1.5.3 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 (71%, 72.5% and 57.0% in arip10, 30 mg, and the placebo arm respectively). A greater percentage of subjects (7.0%) in the aripiprazole 10 mg arm experienced severe TEAEs than did subjects in the aripiprazole 30 mg arm (3.9%) or in the placebo arm (3.0%). The majority of TEAEs were mild or moderate in severity.

7.1.5.4 Common adverse event tables

Table 17 summarizes the most commonly reported TEAEs by ≥ 5% incidence in any treatment arm.

Table 17 Most Commonly Reported TEAEs by ≥ 5% in Any Treatment Group

Class and MedDRA Preferred Term	Aripiprazole 10 mg (N = 100) n (%)	Aripiprazole 30 mg (N = 102) n (%)	Placebo (N = 100) n (%)	Total (N = 302) n (%)
Total subjects with at least one TEAE	71 (71.0)	74 (72.5)	57 (57.0)	202 (66.9)
Gastrointestinal Disorders				
Nausea	9 (9.0)	10 (9.8)	6 (6.0)	25 (8.3)
Vomiting	5 (5.0)	3 (2.9)	5 (5.0)	13 (4.3)
Infections and Infestations				
Nasopharyngitis	5 (5.0)	5 (4.9)	4 (4.0)	14 (4.6)
Nervous System Disorders				
Akathisia	5 (5.0)	12 (11.8)	5 (5.0)	22 (7.3)
Dizziness	7 (7.0)	4 (3.9)	3 (3.0)	14 (4.6)
Extrapyramidal disorder	13 (13.0)	22 (21.6)	5 (5.0)	40 (13.2)
Headache	16 (16.0)	11 (10.8)	10 (10.0)	37 (12.3)
Somnolence	11 (11.0)	22 (21.6)	6 (6.0)	39 (12.9)
Tremor	2 (2.0)	12 (11.8)	2 (2.0)	16 (5.3)
Psychiatric Disorders				
Agitation	1 (1.0)	3 (2.9)	5 (5.0)	9 (3.0)
Insomnia	11 (11.0)	10 (9.8)	15 (15.0)	36 (11.9)

7.1.5.5 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.

7.1.5.6 Additional analyses and explorations

7.1.5.6.1 Extrapyramidal Symptom Rating Scales

The Simpson-Angus Scale (SAS) total score, Barnes Akathisia Rating Scale (BARS) global score and Abnormal Involuntary Movement Scale (AIMS) movement rating score were conducted to assess extrapyramidal adverse events. The data were analyzed by week in both LOCF and OC population. Although some differences between the aripiprazole treatment arms and placebo arms reached statistical significance, these changes were not considered clinically meaningful.

Change from Baseline in SAS Total Score
At baseline, the mean SAS Total Scores ranged from 10.6 to 11.1 across treatment arms. Statistically significant mean increases in parkinsonian symptoms compared to placebo were

observed in the aripiprazole 10 mg arm at Weeks 4, 5, and 6, and for placebo over the aripiprazole 30 mg arm at Weeks 2, 3, 4, 5, and 6 (LOCF and OC).

Change from Baseline in BARS Global Score
At baseline, the mean BARS Global Score was 0.1 across treatment arms. A statistically significant mean increase in akathisia symptoms compared to placebo was observed in the aripiprazole 30 mg arm at Week 2 using the LOCF data set.

Change from Baseline in AIMS Movement Rating Score
Small improvements (ie, decreases) in the mean AIMS Movement Rating Scores were seen in the aripiprazole 10 mg and 30 mg arms using the LOCF and OC datasets. The greatest mean changes (decrease) from baseline were in the aripiprazole 10 mg arm at Weeks 4, 5, and 6; the difference from placebo was statistically significant at Week 5 ($p = 0.0486$; LOCF). No statistically significant differences between treatment arms were observed using the OC dataset.

7.1.6 Less Common Adverse Events

No less common adverse events of significant concern were identified in these studies.

7.1.7 Laboratory Findings

7.1.7.1 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 change from baseline to endpoint, treatment-emergent abnormalities at any time and treatment-emergent potentially clinically significant abnormalities for each laboratory analyte were analyzed separately.

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

Study 31-03-239 is the only acute, controlled study submitted to this sNDA. Therefore, only laboratory data from Study 31-03-239 were reviewed in detail in this safety review. Safety data from Study 31-03-241, an open label, long term safety study, were used to detect rare, and unexpected serious clinically significant laboratory abnormalities.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Serum Chemistry
No clinically relevant mean changes were observed for any of the serum chemistry laboratory tests. There were no dose-related trends observed in the serum chemistry test abnormalities

reported as TEAEs. None of these TEAEs were reported as SAEs or resulted in discontinuation of study medication.

Hematology
No clinically relevant mean changes were observed for any of the hematology laboratory tests. Two abnormal hematology laboratory test results were reported as TEAEs: increased eosinophil count and increased glycosylated haemoglobin (1 subject each in the aripiprazole 10 mg arm). Neither of these TEAEs was reported as an SAE or resulted in discontinuation of study medication.

Urinalysis
No clinically relevant mean changes were observed for any of the urinalysis laboratory tests. One abnormal urinalysis laboratory test results was reported as a TEAE: asymptomatic bacteriuria (2 subjects in the placebo arm). This TEAE was not an SAE nor did it result in discontinuation of study medication.

Insulin
No clinically relevant mean changes were observed in the insulin or fasting insulin results. Two abnormal insulin laboratory test results were reported as TEAEs: increased blood insulin (2 subjects in the aripiprazole 10 mg arm) and hyperinsulinemia (1 subject in the aripiprazole 10 mg arm). Neither of these TEAEs was reported as an SAE or resulted in discontinuation of study medication.

Prolactin
A mean decrease in prolactin levels relative to baseline was observed overall across all treatment groups. The mean change from baseline to endpoint in prolactin levels was -8.82 ng/mL, -11.94 ng/mL, and -16.74 ng/mL in the placebo, aripiprazole 10 mg, and aripiprazole 30 mg arms, respectively.

When analyzed by gender, similar pattern were observed for males (−4.21 ng/mL, −9.62 ng/mL, and −14.69 ng/mL in the placebo, arip 10 mg, and arip 30 mg arms, respectively). For females, the decreases in prolactin levels were greater than for males in all treatment arms, especially in placebo arm (−15.81 ng/mL, −13.70 ng/mL, and −20.62 ng/mL in the placebo, arip 10 mg, and arip 30 mg arms, respectively).

The clinical significance of decrease in prolactin level is unclear. Since majority patients have been exposed to different antipsychotics right before this study (3 days washout period before given study medications and 74% patients have received treatment for previous episodes), the decrease in prolactin level in this study may be partly caused by discontinuation of prolactin increasing antipsychotics, such as risperidone.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 18 summarizes incidence of potentially clinically significant laboratory test abnormalities. The most commonly reported potentially clinically significant laboratory test abnormalities (by ≥

3% incidence in any treatment group) were: ALT, total bilirubin, total CPK, eosinophils (%) and prolactin. Overall, no clinically meaningful trends were observed for any of the potentially clinically significant laboratory test abnormalities.

Table 18 Incidence of Potentially Clinically Significant Laboratory Test Abnormalities

Test (Units)[a]	Aripiprazole 10 mg (N = 100)		Aripiprazole 30 mg (N = 102)		Placebo (N = 100)		Total (N = 302)	
	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]
Chemistry								
ALT (IU/L)	98	3 (3.1)	95	2 (2.1)	96	0 (0.0)	289	5 (1.7)
AST (IU/L)	98	2 (2.0)	95	1 (1.1)	96	0 (0.0)	289	3 (1.0)
Bilirubin, total (mg/dL)	98	1 (1.0)	95	4 (4.2)	96	2 (2.1)	289	7 (2.4)
CPK, total (IU/L)	98	5 (5.1)	95	7 (7.4)	96	5 (5.2)	289	17 (5.9)
Potassium (mEq/L)	98	0 (0.0)	95	0 (0.0)	96	1 (1.0)	289	1 (0.3)
Uric acid (mg/dL)	98	1 (1.0)	95	0 (0.0)	96	1 (1.0)	289	2 (0.7)
Hematology								
Eosiniphils (%)	95	7 (7.4)	93	2 (2.2)	93	3 (3.2)	281	12 (4.3)
Hematocrit (%)	95	0 (0.0)	93	0 (0.0)	94	1 (1.1)	282	1 (0.4)
Hemoglobin (g/dL)	95	2 (2.1)	93	0 (0.0)	94	1 (1.1)	282	3 (1.1)
WBC (thous/μL)	95	0 (0.0)	93	1 (1.1)	94	1 (1.1)	282	2 (0.7)
Other								
Prolactin (ng/mL)	98	3 (3.1)	95	0 (0.0)	96	6 (6.3)	286	9 (3.1)

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

No any SAEs were caused by laboratory abnormalities and no cases were discontinued due to laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

Metabolic Syndrome Evaluation
The analyses on the mean changes from baseline in fasting triglycerides, fasting HDL-C levels, fasting glucose levels, waist circumference, BMI and blood pressure were performed. Overall, no clinically meaningful changes from baseline were observed in any of the above metabolic syndrome evaluation parameters for males or females.

The incidences of metabolic syndrome abnormalities were also analyzed. Overall at the last visit, no clinically meaningful trends were observed in the incidences of abnormalities for fasting triglyceride levels, fasting HDL-C levels, fasting glucose levels, supine systolic or diastolic BP, and standing systolic and diastolic BP. The fasting triglyceride levels, fasting HDL-C levels, fasting glucose levels and BMI for all subjects were presented in Table 20. The criteria for above metabolic measures are presented in Table 19.

Table 19 Criteria for Metabolic Syndrome Abnormalities

Parameter	Age	Criterion Value
Serum fasting triglycerides (mg/dL)	12 – 19 years	≥ 110 mg/dl
Serum fasting HDL-C (mg/dL)	12 – 19 years	≤ 40 mg/dL
Serum fasting glucose (mg/dL)	12 – 19 years	≥ 110 mg/dL
BMI	12 – 19 years	> 95th percentile within the same age and gender population

Table 20 Incidence of Fasting Triglyceride, HDL, Glucose Abnormalities for All Subjects

Parameter	Visit	Aripiprazole 10 mg N=100		Aripiprazole 30 mg N=100		Placebo N=100	
		N	n (%)	N	n (%)	N	n (%)
Fasting Triglyceride (mg/dL)	Baseline	50	17(34.0)	49	17(34.7)	51	22(43.1)
	Day 42	51	17(33.3)	40	12(30.0)	44	16(36.4)
	Last visit	59	18(30.5)	49	16(32.7)	50	17(34.0)
Fasting HDL-C level (mg/dL)	Baseline	50	13(26.0)	49	10(20.4)	51	16(31.4)
	Day 42	51	13(25.5)	40	10(25.0)	44	16(36.4)
	Last visit	59	14(23.7)	49	12(24.5)	50	20(40.0)
Fasting glucose level (mg/dL)	Baseline	69	4(5.8)	69	1(1.4)	70	4(5.7)
	Day 42	73	2(2.7)	70	0(0.0)	75	2(2.7)
	Last visit	86	2(2.3)	79	0(0.0)	88	2(2.3)
BMI (kg/cm^2)	Baseline	100	20(20)	102	13(12.7)	100	13(13.0)
	Day 42	84	12(14.3)	84	10(11.9)	89	12(13.5)
	Last visit						

N is the total number of subjects with postbaseline results at the visit.
n is the number of subjects meeting the criteria for potential clinical significance.

7.1.7.5 Special Assessments

No special assessments were warranted in this study.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The potential treatment effect on mean change from baseline to Day 42 and last visit, 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.

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

Study 31-03-239 is the only acute, controlled study submitted to this sNDA. Therefore, only vital signs data from Study 31-03-239 were reviewed in detail in this safety review. Safety data from Study 31-03-241, an open label, long term safety study, were used to detect rare, and unexpected serious, clinically significant vital sign abnormalities.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The analyses on the mean changes from baseline in vital signs parameters (weight, BMI, waist circumference, body temperature, respiration rate, supine and standing heart rate, supine and standing BP) were performed. No clinically relevant mean changes from baseline were observed in vital signs parameters.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following abnormal vital sign findings were reported as TEAEs: palpitations and postural orthostatic tachycardia syndrome (1 each in the aripiprazole 30 mg arm); tachycardia (2 in the aripiprazole 10 mg arm); pyrexia (1 in the aripiprazole 10 mg arm, 3 in the aripiprazole 30 mg arm, and 2 in the placebo arm); increased body temperature (1 in the aripiprazole 10 mg arm and 1 in the placebo arm); hot flush (1 in the aripiprazole 10 mg arm); hypotension (2 in the aripiprazole 30 mg arm and 1 in the placebo arm); and orthostatic hypotension (3 in the aripiprazole 30 mg arm).

At the last visit, the percentage of subjects who experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline) was 4/99 (4.0%) in the aripiprazole 10 mg arm, 5/97 (5.2%) in the aripiprazole 30 mg arm, and 1/98 (1.0%) in the placebo arm. The percentage of subjects who experienced a potentially clinically significant weight loss (≥ 7% weight loss compared to baseline) at the last visit was 3/99 (3.0%) in the aripiprazole 10 mg arm, 2/97 (2.1%) in the aripiprazole 30 mg arm, and 6/98 (6.1%) in the placebo arm.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

None of treatment-emergent vital signs abnormalities were reported as SAEs or resulted in discontinuation of study medication.

7.1.8.4 Additional analyses and explorations

Weight and BMI Z-scores

The mean changes from baseline for weight (see Table 21) and BMI z-scores (see Table 22) for Day 42 and last visit were within 0.5 SD of the general population for all three treatment arms, and the changes from baseline were negligible. At the last visit, the mean (SD) in weight z-score was 0.00 (0.28) with a range of −1.31 to 1.54 in the aripiprazole 10 mg arm; 0.00 (0.20) with a range of −0.76 to 0.46 in the aripiprazole 30 mg arm; and −0.11 (0.22) with a range of −0.98 to 0.39 in the placebo arm. At the last visit, the mean (SD) in BMI z-score was 0.01 (0.26) with a range of −1.08 to 1.07 in the aripiprazole 10 mg arm; 0.01 (0.25) with a range of −1.07 to 0.80 in the aripiprazole 30 mg arm; and −0.12 (0.27) with a range of −0.99 to 0.56 in the placebo arm.

Similar results were observed for the mean change from baseline in BMI z-scores for males and for females.

Table 21 Mean Change from Baseline in Weight Z-scores

Treatment	Visit	n	Mean (SD)	Change from Baseline		
				n	Mean (SD)	Range
Arip 10 mg	Baseline	100	0.14 (1.42)			
	Day 42	84	0.14 (1.27)	84	0.03 (0.26)	-0.56 – 1.54
	Last Visit	99	0.13 (1.37)	99	0.00 (0.28)	-1.31 – 1.54
Arip 30 mg	Baseline	102	0.26 (1.28)			
	Day 42	84	0.25 (1.31)	84	-0.00 (0.21)	-0.76 – 0.46
	Last Visit	97	0.28 (1.28)	97	0.00 (0.20)	-0.76 – 0.46
Placebo	Baseline	100	0.25 (1.14)			
	Day 42	89	0.13 (1.19)	89	-0.12 (0.22)	-0.98 – 0.39
	Last Visit	98	0.17 (1.17)	98	-0.11 (0.22)	-0.98 – 0.39

Table 22 Mean Change from Baseline in Body Mass Index Z-scores

Treatment	Visit	n	Mean (SD)	Change from Baseline		
				n	Mean (SD)	Range
Arip 10 mg	Baseline	100	0.35 (1.30)			
	Day 42	84	0.31 (1.19)	84	0.03 (0.24)	-0.60 – 1.07
	Last Visit	99	0.34 (1.26)	99	0.01 (0.26)	-1.08 – 1.07
Arip 30 mg	Baseline	102	0.39 (1.08)			
	Day 42	84	0.38 (1.05)	84	0.01 (0.26)	-1.07 – 0.80
	Last Visit	97	0.41 (1.03)	97	0.01 (0.25)	-1.07 – 0.80
Placebo	Baseline	100	0.35 (1.12)			
	Day 42	89	0.21 (1.20)	89	-0.13 (0.27)	-0.99 – 0.56
	Last Visit	98	0.25 (1.18)	98	-0.12 (0.27)	-0.99 – 0.56

In the 6-month, long-term safety study (31-03-241), the mean changes from baseline for weight, BMI, and height z-scores for each visit were within 0.5 standard deviations of the general population. This was also true of BMI z-scores when analyzed by gender. No clinically meaningful changes were observed in weight z-scores or BMI z-scores or in the overall evaluation.

7.1.9 Electrocardiograms (ECGs)

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

Mean change, treatment-emergent ECG abnormalities, and treatment-emergent potentially clinically significant ECG abnormalities were summarized and compared across treatment groups. No clinically meaningful ECG abnormalities were observed.

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

Study 31-03-239 is the only acute, controlled study submitted to this sNDA. Therefore, only ECG data from Study 31-03-239 were reviewed in detail in this safety review. Safety data from

Study 31-03-241, an open label, long term safety study, were used to detect rare and unexpected serious clinically significant ECG abnormalities.

For the analysis of QT and QTc the following correction methods were used by the sponsor:

- QTcB is the corrected (for heart rate) QT interval by the Bazett formula: $QTcB=QT/(RR)_{0.5}$
- QTcF is the corrected (for heart rate) QT interval by the Fridericia formula: $QTcF=QT/(RR)_{0.33}$, and
- QTcE is the corrected (for heart rate) QT interval by the general fractional exponent correction method, i.e., $QTcF= QT/(RR)_k$. The value of k will be determined by fitting the regression equation log(QT)=constant + klog(RR) using the pre-treatment (QT,RR) data of all subjects.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

The changes from baseline in ECG parameters (including ventricular rate, PR interval, RR interval, QRS interval, and QT interval) were analyzed and no clinically significant mean changes from baseline were observed.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The incidences of potentially clinically significant changes in ECG parameters are summarized in Table 23. Overall, no clinically meaningful trends were observed for any of the potentially clinically significant changes in ECG parameters.

Table 23 Incidence of Potentially Clinically Significant Changes in ECG Parameters

Type/Abnormality	Aripiprazole 10 mg (N = 100)		Aripiprazole 30 mg (N = 102)		Placebo (N = 100)		Total (N = 302)	
	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]
Rhythm								
Sinus bradycardia	92	2 (2.2)	92	1 (1.1)	89	1 (1.1)	273	4 (1.5)
Supraventricular premature beat	92	0 (0.0)	92	2 (2.2)	89	2 (2.2)	273	4 (1.5)
ST/T Morphology								
Myocardial ischemia	92	1 (1.1)	92	0 (0.0)	89	0 (0.0)	273	1 (0.4)
QTcB	92	2 (2.2)	92	3 (3.3)	89	3 (3.4)	273	8 (2.9)

[a] Ne is the total number of subjects with at least one postbaseline numeric result for the given parameter.
[b] n is the number of subjects with a potentially clinically significant ECG test abnormality.

The following ECG abnormalities were reported as TEAEs: sinus bradycardia (1 subject each in the aripiprazole 10 mg and 30 mg arms); supraventricular extrasystoles (1 subject each in the aripiprazole 30 mg arm and the placebo arm); wandering pacemaker (1 subject in the 30 mg aripiprazole arm); abnormal electrocardiogram T wave (1 subject in the placebo arm).

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

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

7.1.9.4 Additional analyses and explorations

Additional ECG QT Interval Analyses

A summary of mean change from baseline in QT and QTc interval at Day 42 and last visit is presented in Table 24. Overall, greater decreases in mean QT and QTc intervals from baseline to Day 42 and the last visit were seen in the 30 mg aripiprazole arm compared to the placebo arm. Differences between changes from baseline in the 30 mg aripiprazole arm and placebo arm were statistically significant for all QT and QTc variables at both time points. I discussed this issue (QT shortening) with Dr. Stephen Grant, a medical reviewer in QT-team, the Division of Cardiovascular-Renal Drug Products (DCRDP), and Dr. Norman Stockbridge, director of DCRDP. They felt that at this time point no QT consultation is necessary and no any regulatory actions are recommended because the QT interval shortness in this study were very small (< 7 Msec) and the clinical significance of shortening QT interval is remained unclear at this time.

Table 24 Mean Change from Baseline in QT and QTc Intervals at Day 42 and Last Visit (Msec)

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
QT								
Day 42	81	1.66	83	-1.14	80	7.75	0.0804	0.0106
Last Visit	91	-0.21	92	-2.29	87	5.73	0.0742	0.0159
QTcB[c]								
Day 42	81	-1.06	83	-6.93	80	0.34	0.5799	0.0039
Last Visit	91	-0.98	92	-5.58	87	-0.02	0.6881	0.0199
QTcF[c]								
Day 42	81	0.08	83	-4.82	80	2.87	0.1444	<.0001
Last Visit	91	-0.62	92	-4.37	87	1.94	0.1564	0.0005
QTcN[c]								
Day 42	81	-0.27	83	-5.22	80	2.47	0.1612	<.0001
Last Visit	91	-0.78	92	-4.54	87	1.65	0.1872	0.0008
QTcE[c]								
Day 42	81	0.03	83	-4.63	80	3.00	0.1216	<.0001
Last Visit	91	-0.64	92	-4.21	87	2.05	0.1360	0.0006

7.1.10 Immunogenicity

Immunogenicity was not studied in these studies.

7.1.11 Human Carcinogenicity

Human carcinogenicity was not studied in these studies.

7.1.12 Special Safety Studies

No special safety studies were deemed necessary.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

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

7.1.14 Human Reproduction and Pregnancy Data

No pregnancies were reported in this study.

7.1.15 Assessment of Effect on Growth

The mean changes from baseline for weight and BMI z-scores (see 7.1.8.4 Additional Analyses and Exploration/Weight and BMI Z-scores Table 21 and Table 22) for each visit in Study 31-03-239 were within 0.5 SD of the general population for all three treatment arms, and the changes from baseline were negligible. Therefore, no significant effect on growth from aripiprazole acute treatment was observed.

In the 6-month, long-term safety study (31-03-241), the mean changes from baseline for weight, BMI, and height z-scores for each visit were within 0.5 standard deviations of the general population. Because there was no control arm in this study, it is difficult to interpret the data from this study.

7.1.16 Overdose Experience

No aripiprazole overdose experience was reported in these studies.

7.1.17 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 (b) (4) 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 31-03-239 is a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in adolescent patients, ages 13 to 17 years, with a DSM-IV diagnosis of schizophrenia.

A total of 302 subjects were randomized and treated in this study: 100/302 (33.1%) in the aripiprazole 10 mg arm, 102/302 (33.8%) in the aripiprazole 30 mg arm, and 100/302 (33.1%) in the placebo arm. Of these, 93/302 (30.8%) were randomized in the US, 141/302 (46.7%) were randomized in Europe, and 68/302 (22.5%) were randomized in other regions. All randomized subjects were included in the efficacy and safety analyses.

A total of 258/302 (85.4%) subjects completed the study: 84/100 (84.0%) in the aripiprazole 10 mg arm, 84/102 (82.4%) in the aripiprazole 30 mg arm, and 90/100 (90.0%) in the placebo arm.

7.2.1.2 Demographics

The three treatment arms in Study 31-03-239 were demographically similar and had similar baseline disease characteristics. The majority of subjects were male (171/302, 56.6%), and Caucasian (180/302, 60.0%). Male and Caucasian population were slightly lower respectively in Aripiprazole 10 mg arm (45%, 54%) compare to Aripiprazole 30 mg (63.7%, 64.0%) or placebo (61%, 60%) arm. The mean age was 15.5 years. The baseline disease severity was comparable across all treatment arms. The mean PANSS Total Score and CDRS-R Suicidal Ideations Score was 94.1 and 1.3, respectively. A total of 223/302 (74.0%) subjects had received treatment for previous episodes.

7.2.1.3 Extent of exposure (dose/duration)

A total of 202 subjects were exposed to aripiprazole in Study 31-03-239: 100 in the 10 mg arm at average doses ranging from 6.2 mg to 10.0 mg, and 102 in the 30 mg arm at average doses ranging from 6.9 mg to 30.0 mg. A total of 100 subjects were exposed to placebo. The percentage of subjects exposed to study drug for 36 to 42 days was 86/100 (86.0%) in the aripiprazole 10 mg arm at an average dose of 9.5 mg; 84/102 (82.4%) in the aripiprazole 30 mg arm at an average dose of 27.8 mg; and 90/100 (90.0%) in the placebo arm. Approximately one-third of subjects in all treatment groups were exposed to study medication beyond the planned 42-day treatment period. Table 25 summarizes subject exposure to aripiprazole or placebo in Study 31-03-239.

Table 25 Extent of Exposure to Study Medication in Study 31-03-239

Study Days	Aripiprazole 10 mg N = 100		Aripiprazole 30 mg N = 102		Placebo N = 100
	n (%)	Average dose (mg)	n (%)	Average dose (mg)	n (%)
36 - 42 Days	86 (86.0)	9.5	84 (82.4)	27.8	90 (90.0)
Fixed dose period	99 (99.0)	9.8	94 (92.2)	28.9	97 (97)
Overall	100 (100)	8.9	102 (100.0)	22.5	100 (100.0)

As of the clinical data cut-off date of 09 Nov 2006, long-term safety data were available from 281 adolescent subjects with schizophrenia that received oral aripiprazole in Studies 31-03-239 and/or 31-03-241. Of these subjects, 147 (52.3%) were exposed to aripiprazole for ≥ 26 weeks and 196 (69.8%) for > 20 weeks. This adolescent population represents a cumulative exposure to aripiprazole of 119 subject-years. Subjects in the long-term analysis received an average aripiprazole dose of 16.1 mg daily, ranging from 2.0 to 28.8 mg. Of the subjects treated for ≥ 26 weeks, 34.0% received an average daily dose of ≥ 20 mg.

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 7.1.17 Postmarketing experience

7.2.2.3 Literature

See 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 adolescents.

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 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

Study 31-03-238, a pharmacokinetic study, is submitted to this sNDA and Andre J. Jackson, PhD is the primary Bio-Pharm reviewer for this study. Up to time of completion of this review, Dr. Jackson's review is still pending.

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 Adequacy 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 one patient (subject 03239-356-3045, 10% of the 10 patients with submitted CRFs), whom I randomly selected from the database from Study 31-03-239. The AE data listings examined were AE0.xpt from 31-03-239 datasets. The consistency of adverse event 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.

Two study sites (Site 074 and 104) in Study 31-03-239 were selected for scientific inspection by DSI. The inspection found a few minor deficiencies of data in each study site. But, the inspector felt that the deficiencies were unlikely to have an effect on data reliability.

7.2.9 Additional Submissions, Including Safety Update

No additional safety submissions, including safety update were submitted to this NDA during review period.

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

Based on a comparison of the results of five short-term adult studies in schizophrenia with the results of this pediatric schizophrenia study, the safety profile of aripiprazole in adolescents with the diagnosis of schizophrenia is comparable to the adult schizophrenia population, with the exception of dose-related occurrence of higher frequency of somnolence and extrapyramidal symptoms observed in the pediatric population.

The study design and drug exposure in Study 31-03-239 and 31-23-241 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

Only one acute controlled study (Study 31-03-239) and one long term open-labeled safety study (Study 31-03-241) were submitted to this sNDA. No data were pooled across studies.

7.4.1.2 Combining data

No combining 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 was 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 31-03-239 is a 6-week, fixed-dose study containing 3 arms—aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms. All study medications were administered orally.

Study 31-03-241 is a 6-month, flexible-dose study. Doses of aripiprazole 2 mg to 30 mg 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 these topics from this submission.

8.3 Special Populations

See 8.4 Pediatrics.

8.4 Pediatrics

This submission contains three children and adolescents clinical studies—one PK study, one acute efficacy and safety study and one long term open-labeled safety study. The efficacy and safety data from Study 31-03-239 and 31-03-241 are comparable to that obtained from adult schizophrenia clinical trials with the exception of dose-related occurrence of higher frequency of somnolence and extrapyramidal symptoms in adolescent population.

8.5 Advisory Committee Meeting

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

8.6 Literature Review

A worldwide literature search for published articles pertaining to the safety and efficacy of aripiprazole was conducted. The literature search timeframe includes published articles from March 1, 2005 through a cut-off date of December 1, 2006.

The Literature Reference Search Conducted by Bristol-Myers Squibb
The literature search was conducted by (b) (6)

Search terms:
ARIPIPRAZOLE, ABILITAT, ABILIFY, OPC-14597 (by searching OPC()14597, it also covers OPC 14597), OPC14597, OPC-31 (by searching OPC()31, it also covers OPC 31), OPC31, 129722-12-9 (Chem. Abs. Registry Number), 156680-99-8 (Chem. Abs. Registry Number)

Databases:
MEDLINE, BIOSIS/Biological Abstracts, EMBASE/EMBASE ALERTS, DRUGU/Derwent Drug File, SCISEARCH/Science Citation Index, CAPLUS/Chemical Abstracts, TOXCENTER,

LIFESCI/Life Sciences Collection, IPA/International Pharmaceutical Abstracts, JICST-EPLUS/Japanese Information Center, ADISCTA: Adis Clinical Trials Insight

The literature references were identified by searching above terms in basic index (as opposed to full text) in the above 11 databases. Please note none of the 10 databases are full text, therefore full text searching was not possible.

The Literature Reference Search Conducted by Otsuka Japan
The literature reference search for aripiprazole was conducted at Pharmacovigilance Department of Otsuka Pharmaceutical Company-Japan (Otsuka Japan). Toshinori Kaneyasu is the person in charge of literature search.

In Japan
Search terms:

- ARIPIPRAZOLE
- Terms related to or suggestive of adverse drug reaction, interaction, addiction/intoxication/poisoning/accidents
- Adverse drug reaction: adverse effects caused by medicinal products including over effect of medicinal product, deficiency because it is not included in ingredients of medicinal product e.g. microelement deficiency, abnormal laboratory data etc..
- Interaction: adverse effects from drug-drug interaction, food-drug interaction_e.g. increase or decrease in blood level of medicinal product(s)
- Addiction/Poisoning/intoxication/accidents: adverse effects from improper use including suicide (attempt) or medication error etc.

Database:
SELIMIC—the database established by the external service provider of Otsuka which covers all major medical scientific literature published in Japan.

Outside Japan in Otsuka Territory
Search terms:
ARIPIPRAZOLE

Database:
Major medical and scientific journals published in each country

Conclusion from Literature Search
The literature contains no findings that would adversely affect conclusions about the safety and efficacy of aripiprazole.

8.7 Postmarketing Risk Management Plan

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

8.8 Other Relevant Materials

No other relevant materials were provided.

9 OVERALL ASSESSMENT

9.1 Conclusions

Aripiprazole was effective in the acute treatment of adolescent subjects with schizophrenia at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared to placebo in PANSS Total Score at Week 6.

Based on safety data from Study 31-03-239 and Study 31-03-241, the safety profile of aripiprazole in adolescents with the diagnosis of schizophrenia is comparable to the adult schizophrenia population, with the exception of dose-related occurrence of higher frequency of somnolence and extrapyramidal symptoms observed in the pediatric population.

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 point.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

9.5 Comments to Applicant

I recommended several changes regarding the proposed labeling. Details can be found in 9.4 Labeling Review.

I also disagree with sponsor's (b) (4) claim. Up to date, the sponsor did not submitted (b) (4) treatment claim.

Final approval of this sNDA is contingent on mutual agreement on labeling (b) (4)

10 APPENDICES

10.1 Investigators And Study Sites

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
001	Paul Ambrosini, MD	Drexel University College of Medicine Department of Psychiatry c/o Friends Hospital 4641 Roosevelt Boulevard Philadelphia, PA 19124 US	0	0
002	J. Robert Batterson, MD	Children's Mercy Hospitals and Clinics 2401 Gillham Road Kansas City, MO 64108 US	1	0
005	Rudy Chavez, MD	Advanced Psychiatric Group 180 North San Gabriel Boulevard Pasadena, CA 91107 US	5	5
006	Robert L. Findling, MD	University Hospitals of Cleveland Division of Child and Adolescent Psychiatry 11100 Euclid Avenue Cleveland, OH 44106-5080 US	4	2
007	Carlos Guerra Jr, MD, PA	9701 Richmond Avenue Suite 200 Houston, TX 77042 US	4	2
008	Sanjay Gupta, MD	Global Research and Consulting 515 Main Street Olean, NY 14760 US	2	0
009	Scott M. Hogan, MD	Pinnacle Point Hospital ATT: Clinical Trials 11501 Financial Center Parkway Little Rock, AR 72211 US	2	1
010	Ali A. Kashfi, MD	597 Maitland Avenue Altamonte Springs, FL 32701 US	2	1

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
011	Alain Katic, MD	Claghorn - Lesem Research Clinic 6750 West Loop South Suite 1050 Bellaire, TX 77401 US	2	2
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 US	1	0
013	Adam F. Lowy, MD	Comprehensive NeuroScience, Inc Psychiatric Institute of Washington, DC 4228 Wisconsin Avenue, NW Washington, DC 20016 US	4	4
015	Denis Mee-Lee, MD	Hawaii Clinical Research Center 1750 Kalakaua Avenue Suite 2602 Honolulu, HI 96826 US	1	1
016	Marino Molina, Jr, MD	Amedica Research Institute, Inc 625 E 49th Street Hialeah, FL 33013 US	4	1
017	Eliot Moon, MD	Elite Clinical Trials, Inc 34859 Fredrick Street Suite 110 & 111 Wildomar, CA 92595 US	3	2
019	Syed J. Mustafa, MD	Pacific Institute of Medical Sciences 10126 NE 132nd Street Suite C Kirkland, WA 98034 US	5	5
020	Steven G. Potkin, MD	UC Irvine Medical Center 101 The City Drive South Orange, CA 92868 US	1	1

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
021	Sohail Punjwani, MD	Professional Clinical Research, Inc c/o Segal Institute for Clinical Research 1065 NE 125th Street Suite 417 North Miami, FL 33161 US	4	1
022	Joachim D. Raese, MD	Behavioral Health 2000, LLC 5945 Brockton Avenue Riverside, CA 92506 US	1	1
023	Rakesh Ranjan, MD	Rakesh Ranjan, MD and Associates, Inc 5010 Mayfield Road Suite 309 Lyndhurst, OH 44124 US	1	1
024	Adelaide S. Robb, MD	Children's National Medical Center 111 Michigan Avenue, NW Washington, DC 20010 US	6	4
025	Russell E. Scheffer, MD	Children's Health System Child & Adolescent Psychiatry and Behavioral Medicine 9000 W Wisconsin Avenue PO Box 1997, MS#750 Milwaukee, WI 53201-1997 US	3	2
026	Michael Schwartz, DO	College Hospital Costa Mesa 301 Victoria Street Costa Mesa, CA 92627 US	0	0
027	Veronique Sebastian, MD	Sooner Clinical Research 5929 N May Avenue Suite 401 Oklahoma City, OK 73112 US	4	3

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
029	Raj Shiwach, MD	Insite Clinical Research 2000 N Old Hickory Trail DeSoto, TX 75115 US	2	2
030	Linmarie Sikich, MD	University of North Carolina at Chapel Hill Department of Psychiatry CB #7160 Chapel Hill, NC 27599-7160 US	1	1
031	Juanita Lynn Taylor, MD	University of Arkansas for Medical Sciences College of Medicine 4301 W Markham Little Rock, AR 72205 US	0	0
032	Roger B. Vogelfanger, MD	Compass Intervention Center 7900 Lowrance Road Memphis, TN 38125 US	4	3
033	Kashinath G. Yadalam, MD	Lake Charles Clinical Trials 2770 3rd Avenue Suite 340 Lake Charles, LA 70601 US	2	2
034	James Knutson, MD	Eastside Therapeutic Resource 512 6th Street South Suite 101 Kirkland, WA 98033 US	1	1
035	Juan B. Espinosa, MD	TuKoi Institute for Clinical Research 20820 West Dixie Highway Miami, FL 33180 US	1	1
036	Paul J. Markovitz, MD	Mood and Anxiety Research, Inc 7409 North Cedar Avenue Suite 101 Fresno, CA 93720 US	1	0

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
037	Robert L. Hendren, DO	University of California Davis Medical Center MIND Institute 2825 50th Street Sacramento, CA 95817 US	0	0
038	Robert L. Jimenez, MD	Synergy Research, Inc, LLC 7272 Wurzbach Road Suite 1003 San Antonio, TX 78240 US	1	1
039	Willis Holloway Jr, MD	Cutting Edge Research Group 6613 N Meridian Avenue Oklahoma City, OK 73116 US	3	2
040	Anjali A. Pathak, MD	A.P. Psychiatric & Counseling Services 5251 Emerson Street Jacksonville, FL 32207 US	0	0
041	Carlos A. Santana, MD	University of South Florida Department of Psychiatry and Behavioral Medicine 3515 East Fletcher Avenue Tampa, FL 33613 US	1	0
045	Iliyan Ivanov, MD	Mount Sinai School of Medicine 1425 Madison Avenue 6th Floor New York, NY 10029 US	1	1
046	Robert B. DeTrinis, MD	1040 Calhoun Street New Orleans, LA 70118 US	0	0
047	Michael J. Rieser, MD, PSC	2801 Palumbo Drive Suite 202 Lexington, KY 40509 US	4	2

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
048	Adly Thebaud, MD	Medical Research Group of Central Florida 2725 Rebecca Lane Suite 107 Orange City, FL 32763 US	6	5
050	Barbara L. Gracious, MD	Department of Psychiatry University of Rochester Medical Center 300 Crittenden Blvd Rochester, NY 14642 US	2	0
051	Poonam Soni, MD	University of Utah School of Medicine Department of Psychiatry 30 North 1900 East Room 5R218 Salt Lake City, UT 84132-2502 US	1	1
053	Ismail B. Sendi, MD, MS	New Oakland Child/Adolsecent and Family Center 42621 Garfield Rd Suite #101 Clinton Township, MI 48038 US	2	2
054	Alan Unis, MD	Sacred Heart Medical Center and Children's Hospital 101 West 8th Avenue Spokane, WA 99204 US	3	2
057	Humberto Quintana, MD	2933 Brakley Avenue, Suite A Baton Rouge, LA 70816-2305 US	3	1
058	James T. Cullinan, DO	314 Smolian Clinic 1700 7th Avenue South University of Alabama at Birmingham Birmingham, AL 35294-0018 US	1	1

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
059	Jean A. Frazier, MD	Cambridge Health Alliance Harvard Medical School 1493 Cambridge Street Cambridge, MA 02139 US	0	0
060	Naveed Iqbal, MD	Advanced Bio-Behavioral Sciences, Inc 5 West Main Street Suite 206 Elmsford, NY 10523 US	4	2
063	Sharon E. Cain, MD	University of Kansas Medical Center 3901 Rainbow Boulevard Kansas City, KS 66160 US	0	0
065	Gregory S. Kaczenski, MD	K & S Professional Research Services, LLC 801 Scott Street Little Rock, AK 72201 US	2	2
066	Saul Helfing, MD	Highline-West Seattle Mental Health Center 2600 Southwest Holden Street Seattle, WA 98126 US	0	0
067	Veena Luthra, MD	Clinical Trial Specialists 1 Belmont Avenue Suite 315 Bala Cynwyd, PA 19004 US	1	1
068	Ashraf Attalla, MD	Ridgeview Institute 4015 South Cobb Drive Suite 100 Smyrna, GA 30080 US	4	1
070	Harinder Grewal, MD	Worldwide Research 1908 Sweetwater Road National City, CA 91950 US	4	4

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
071	Jeanette Cueva, MD	Bioscience Research, LLC 222 West 14th Street New York, NY 10011 US	1	0
073	Ann C. Childress, MD	Center for Psychiatry and Behavioral Medicine, Inc 7351 Prairie Falcon Road Suite 160 Las Vegas, NV 89128 US	2	2
074	Michel Woodbury Fariña, MD	307 Eleanor Roosevelt St San Juan, PR 00918 US	8	8
075	Gloria M. González-Tejera, MD	RCMI Clinical Research Center University District Hospital 1st Floor University of Puerto Rico Medical Sciences Campus San Juan, PR 00936-5067 US	0	0
078	Joseph A. Kwentus, MD	Precise Clinical Research, Inc Brentwood Plaza Suite 1060 3531 Lakeland Drive Flowood, MS 39232 US	0	0
079	Michael A. Bengtson, MD	University of Florida, Department of Psychiatry 1600 SW Archer Road Gainesville, FL 32610 US	1	1
081	Prof Frederick W. Hickling	The Department of Psychiatry The University Hospital of the West Indies Mona Kingston 7 Jamaica West Indies	6	3

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
082	John H. Gilliam, MD	International Clinical Research Associates, LLC 1601 Rolling Hills Drive Suite 201 Richmond, VA 23229 US	3	3
083	Donna J. Scott, MD	Southern Cresent Research 58 Hospital Road Suite 101 Newman, GA 30263 US	1	0
101	Anton Slavchev, MD, PhD	Inpatient Child and Adolescent Psychiatric Clinic Multiprofiled Hospital for Active Treatment "Alexandrovska", 13 "Lunna Paprat" Street 1619 Sofia, Bulgaria	8	8
103	Svetlozar Georgiev, MD	Department of Psychiatry, University Multiprofiled Hospital for Active Treatment "Sveti Georgi" 15A Vassil Aprilov Boulevard 4002 Plovdiv Bulgaria	5	2
104	Stefan Todorov, MD, PhD	Multifunctional Hospital for Active Treatment "St Marina" I Psychiatric Clinical 1 Hristo Smirnenski Street 9010 Varna Bulgaria	12	12
105	Lubomir Jivkov, MD	Regional City Psychiatric Dispensary of Sofia 59 "Ekzarh Jossif" Street 1000 Sofia Bulgaria	0	0

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
106	Nadia Polnareva, MD, PhD	Child and Adolescent Psychiatric Clinic "St Nicolas" University Multi-profiled Hospital for Active Treatment "Alexandrovska" 1, G Sofiisky Street 1431 Sofia Bulgaria	0	0
107	Temenuzhka Dechkova-Novakova, MD	District Psychiatric Dispensary - Rousse 20 "Tutrakan" Boulevard 7003 Rousse Bulgaria	4	4
108	Svetlozar Haralanov, MD, PhD	Second Psychiatric Clinic at Specialised Hospital for Active Treatment in Neurology and Psychiatry "Sveti Naum" Tzarigradsko Shausse Blvd IV km 1113 Sofia Bulgaria	3	3
150	Prof Aneta Lakic	Clinic of Neurology and Psychiatry for Children and Adolescents Dr Subotica 6a 11000 Belgrade Serbia and Montenegro	3	2
151	Prof Dr Smijka Popovic Deusic (current) Prof Ivana Timotijevic (original)	Institute of Mental Health, Palmoticeva 37 11000 Belgrade Serbia and Montenegro	5	4
152	Prof Dr Dragan Mitrovic	Institute of Psychiatry Clinical Center Novi Sad Hajduk Veljkova 1 21000 Novi Sad Serbia and Montenegro	6	6
250	Alan L. Schneider, MD	Gateways Hospital and Mental Health Center 1891 Effie Street Los Angeles, CA 90026 US	3	2

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
350	Dr Satish Girimaji	National Institute of Mental Health and Neuro Sciences (NIMHANS) Bangalore 560029 India	2	2
351	Dr Deepak Gupta	Center for Child Health Sir Gangaram Hospital Rajinder Nagar New Delhi 110060 India	2	1
352	Dr Shrinivasa Bhat U	KS Hegde Medical Academy, Deralkatte Mangalore 575018 India	1	0
353	Dr Nadukuru Nooka Raju	Government Hospital for Mental Care Chinawaltair Visakhapatnam 530017 India	1	1
354	Dr G. Prasad Rao	Asha Hospital, 298, Road No. 14, Banjara Hills Hyderabad 500034 India	13	12
355	Dr Nilesh Shah	Department of Psychiatry 1st Floor, College Building Lok Manya Tilak Municipal Medical College and Lok Manya Tilak Municipal General Hospital Sion Mumbai 400022 India	0	0
356	Dr Savita Malhotra	Department Psychiatry, Postgraduate Institution of Medical Education and Research Chandighar 160012 India	5	5
357	Dr P. C. Shastri	Dr Shastri's Clinic 3/3 Vivina Co-op Housing Society, SV Road Andheri (West) Mumbai 400058 India	3	3

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
358	Dr Ranjive Mahajan	Department of Psychiatry Dayanand Medical College and Hospital Tagore Nagar, Civil Lines Ludhiana 141001 India	5	5
359	Dr T.P. Sudhakar	Department of Psychiatry SV Medical College Tirupati 517507 India	1	1
360	Dr T.S.S. Rao	Department of Psychiatry, JSS Medical College & Hospital, Ramanuja Road Mysore 570004 India	3	3
361	Dr Vihang Vahia	Department of Psychiatry Dr R.N. Cooper General Hospital currently located at V.N. Desai Hospital 11th Road, Santacruze (E) Mumbai 400055 India	0	0
362	Dr Ramanathan Sathianathan	Department of Psychiatry, Madras Medical College & Government Hospital E.V.R. Periyar Salai Chennai, Tamilnadu, 600003 India	5	5
502	José Humberto Nicolini Sánchez, MD	Grupo de Estudios Médicos y Familiares Carracci Carracci 107 Col Insurgentes Extremadura CP 03740 DF México	3	1
504	Rosa Elena Ulloa Flores, MD	Hospital Psiquiátrico Infantil "Dr Juan N. Navarro", Av San Buenaventura 86, Col Belisario Domínguez DF, CP 14080 México	1	1

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
505	José Ontiveros Sánchez de la Barquara, MD	INFOSAME Dr Péna No 122, Col Los Doctores, Monterrey, N.L., 64710 Mexico	1	1
507	Severiano Lozano González, MD	Centro Avanzado de Salud Anímica - CASA Padre Mier Poniente 1015, Col Zona Centro Monterrey, Nuevo León, CP 64000 Mexico	1	0
601	Prof Yury A. Alexandrovsky, MD	City Psychiatric Hospital #12 Volokolamskoy shosse 47 123367, Moscow Russia	5	5
603	Prof Leonid M. Bardenstein, MD	Department of Psychiatry, MSUMS, Mental Hospital #15 Moskvorechye Street 7 115522, Moscow Russia	10	9
604	Prof Yuri V. Popov, MD	Bekhterev Research Institute of Psychiatry and Neurology Bekhterev Street 3 193019, Sanct-Petersburg Russia	10	8
605	Prof Elena A. Grigorieva, MD	Yaroslavl Regional Clinical Psychiatry Hospital, Zagorodny Sad Str 6 150003 Yaroslavl Russia	8	8
606	Prof Kausar K. Yakhin, MD	Kazan City Psychoneurological Hospital ul. Volkov 80 420012 Kazan Russia	8	8
608	Prof Alexander O. Bukhanovsky, MD	Scientific Center of Treatment and Rehabilitation "Phoenix", Voroshilovsky pr. 40/128 344010 Rostov-on-Don Russia	5	5

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
609	Yuri A. Fessenko, MD, PhD	Child Center of Rehabilitation Treatment "Child Psychiatry", Pesochnaya nab. 4 197376 St-Peterburg Russia	6	4
610	Natalya V. Dobrovolskaya, MD	Center of Psychopathology and Cognitive Disorder City Psycho neurologycal Dispenser N° 10 with Hospital Matveyev pereulok 3 190121 Sanct-Petersburg Russia	5	5
611	Evgenia G. Rebrova, MD	Psychiatry Hospital #3 Fermskoe Shosse 36 197341 Sanct-Peterburg Russia	3	2
612	Prof Valery N. Krasnov, MD	Moscow Research Institute of Psychiatry Poteshnaya street 3 107076 Moscow Russia	5	5
613	Prof Igor V. Boyev, MD	Clinic of Borderline Disorders Stavropol Medical Academy ul Lenina 417 Stavropol, 355038 Russia	7	6
615	Prof Alexander K. Zinkovskiy, MD	Regional Clinical Psychiatry Hopsital N°. 1 named after M.P. Litvinov Burashevo, Kalininsky district Tver Region, 170546 Russia	1	1
650	Dr Victor Marinescu	Spitalul Clinic de Psihiatrie "Dr Alexandru Obregia" Departmentul 9, sos. Berceni nr. 10-12, Sector 4 041914 Bucuresti Romania	0	0

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
651	Prof Dr Doina Cosman, MD	Clinica de Psihiatrie nr 3 Spitalul Judetean de Urgenta str. Babes nr. 43 400012 Cluj-Napoca Romania	0	0
652	Prof Dr Aurel Nirestean,	Clinica de psihiatrie nr 2, Spitalul Judetean de Urgenta str Gheorghe Marinescu nr. 38 540139 Tirgu Mures Romania	2	2
653	Prof Dr Iuliana Dobrescu	Spitalul Clinica de Psihiatrie "Dr Alexandru Obregia" Clinica de Psihiatrie a Copilului si adolescenti, Sos Berceni nr. 10-12 sector 4 041914 Bucuresti Romania	9	8
654	Dr Bogdan Pacala	Spitalul Clinic de Psihiatrie "Dr Gheorghe Preda" str. Bagdazar nr. 12 550082 Sibiu Romania	0	0
701	Alberto Manuel Bertoldi	Clínica Privada San Agustín Calle 55 N° 763 La Plata Buenos Aires Argentina C.P. 1900	5	5
703	Gustavo Martin Petracca	Instituto Neurociencias Buenos Aires (INEBA) Guardia vieja 4435, C1192AAW Ciudad Autonoma de Buenos Aires Argentina	0	0
704	Carlos Alberto Morra	Sanatorio Morra, Av Sagrada Familia y Nazareth, Barrio Urca Córdoba (5009) Argentina	2	1
705	Roxana Beatriz Galeno	Instituto Neurociencias, Olegario V. Andrade N° 290 Ciudad de Mendoza, Mendoza Argentina (5500)	5	5

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
707	Rolando Dante Salinas	SYTIUM Beruti 2522 P6 (C1425) Capital-Federal, Buenos Aires Argentina	1	1
709	Ricardo Marcelo Corral	Centro de Neuropsiquiatría Marcelo T de Alvear 2430 5° A, (C1122AAN), Buenos Aries Argentina	2	2
710	Julio José Herrera	Centro de Psiquiatría Biológica Pedro Molina 249 1° piso Oficina 2, Ciudad de Mendoza, Mendoza (5500) Argentina	1	1
711	Miguel Márquez, MD	CRF Investigaciones Clínicas Juncal 802 2 "F" Ciudad Autónoma de Buenos Aires Argentina (C1062ABF)	1	0
750	Prof Soo-Churl, Cho	Division of Child and Adolescent Psychiatry Seoul National University Hospital 28 Yeongun-dong, Jongno-gu Seoul, South Korea 110-744	0	0
754	Prof Jae-Min, Kim	Department of Psychiatry, Chonnam National University Hospital 8 Hak-dong, Dong-gu Gwang-ju, South Korea 501-757	1	1
755	Associate Prof Sung-Hoon, Jeong	Department of Psychiatry, Kyungpook National University Hospital 50 Samdeok-2ga Dae-gu, South Korea 700-721	0	0
756	Associate Prof Jeong-Seop, Lee	Department of Pyschiatry Inha University Hospital 7-206, 3-ga, Shinheung-dong Jung-gu Incheon, South Korea 400-711	2	1

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
757	Associate Prof Dong-Ho, Song	Department of Psychiatry Yongdong Sevrance Hospital 146-92, Dogok-dong Kangnam-gu Seoul, South Korea 135-720	0	0
758	Prof Keun-Ah, Cheon	Department of Psychiatry, Kwandong University MyungJi Hospital 2Fr. 697-24, Hwajung-dong Koyang-si Kyunggi-do, South Korea 412-270	0	0
759	Assistant Prof Ji-Hoon, Kim	Department of Psychiatry, 2F Pusan National University Hospital 1-10 Ami-Dong, Seo-gu Pusan, South Korea 602-791	2	2
802	Prof Dr SC. Goran Dodig, MD	Clinical Hospital Split Psychiatric Clinic Spinčićeva 1 21000 Split Croatia	2	2
803	Pavo Filakovic, MD, PhD	Psychiatric Clinic Clinical Hospital Osijek 31000 Osijek, Huttlerova 4 Croatia	3	3
805	Dubravka Kocijan-Hercigonja, MD, PhD	Polyclinic for Neurology and Psychiatry 10000 Zagreb, Kranjceviceva 8 Croatia	2	2
806	Prof Dr Tanja Franciskovic (current) Ljiljana Moro (original)	KBC Rijeka Clinic for Psychiatry Cambierieva 17/7, 51000 Rijeka Croatia	2	2

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
807	Neven Henigsberg	Poliklinika Neuron Croatian Institute for Brain Research, University of Zagreb Medical School, University of Zagreb Salata 12, 10000 Zagreb Croatia	1	0
841	Professor G.A.D. Hart	Room 202 Sandton Medical Center North Block 3 Main Road, Bryanston 2021 South Africa	0	0
842	Dr Prema R. Laban	Crompton Medical Centre West Crompton Street Pinetown 3610 South Africa	2	2
843	Dr L. Nel	Dey Clinic 345 Dey Street Nieuw Muckleneuk 0181 South Africa	3	3
844	Professor C.A. Gagiano	Westdene Research Center 32 Pres. Steyn Avenue Westdene Bloemfontein 9301 South Africa	0	0
845	Dr C.F. Weyers	Calmdene Research Unit 1 Haarburger Crescent Westdene Bloemfontein 9301 South Africa	0	0
850	Prof Valeriy N. Kuznetsov, MD, PhD	Kiev Medical Academy of Postgraduate Education Dept of Psychiatry Psychiatric Hospital No.1 103-A Frunze Str 04080 Kiev Ukraine	4	4

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
851	Prof Oleg Sosontovich Chaban, MD, PhD	Neuroses and Somatoform Disorders Clinic, Ukrainian Research Institute of Social, Forensic Psychiatry and Drug Abuse 1st Road Hospital 8A M.Kotsubinskogo Str Kiev, 03049 Ukraine	4	4
855	Prof Kazakova Svitlana Yevgenivna, MD, PhD	Lugansk Regional Clinical Psychoneurological Hospital, Department of Psychiatry of Lugansk State Medical University 22, 50 let Oborony Luganska, Lugansk, 91045 Ukraine	3	3
856	Prof Valeriy Bitenskyy	Psychiatry Department Odessa State Medical University 9 Acad. Vorobjova Str Odessa 65006 Ukraine	1	1
858	Prof Pidkorytov Valeriy S., MD PhD	Department of Clinical, Social and Child Psychiatry Institute of Neurology, Psychiatry and Narcology AMS of Ukraine 46 Acad. Pavlova Str Kharkiv 61068 Ukraine	2	2
859	Dr Svitlana M. Moroz, PhD	Psychosomatic Center of Dnipropetrovsk Regional Clinical Hospital Oktyabrska sq,14 Dnepropetrovsk 49616 Ukraine	1	1
913	Michael Plopper, MD	Sharp Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, CA 92123 US	1	0

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 US	1	0

10.2 Appendix To Integrated Review of Efficacy

Table 26 Mean Change from Baseline in PANSS Total Score by Week (OC)

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
TREATMENT GROUP	N	MEAN	N	LSMEAN[1]	N	LSMEAN[1]	N	LSMEAN[1]	N	LSMEAN[1]	N	LSMEAN[1]	N	LSMEAN[1]
ARIP-10MG	99	93.7	98	-6.9	97	-14.0	88	-20.1	87	-24.0	86	-27.6	84	-30.6
ARIP-30MG	97	94.9	95	-10.4	93	-15.7	90	-23.4	85	-26.4	84	-30.4	84	-31.9
PLACEBO	98	95.0	97	-7.2	95	-12.3	93	-17.9	91	-19.3	88	-21.7	90	-22.3

2-SIDED P-VALUES[2] FOR PAIRWISE COMPARISONS WITH PLACEBO

ARIP-10MG VS PLACEBO	0.5375	0.8390	0.4001	0.3528	0.0347	0.0124	0.0011
ARIP-30MG VS PLACEBO	0.9372	0.0465	0.1108	0.0200	0.0016	0.0003	0.0002

REFERENCES

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/s/

Jing Zhang
9/14/2007 10:05:09 AM
MEDICAL OFFICER

Mitchell Mathis
9/14/2007 01:10:25 PM
MEDICAL OFFICER
See my Memo to File