U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-463 / S021
Drug Name:	Abilify (Aripiprazole)
Indication(s):	Bipolar I Disorder, Adolescent
Applicant:	Otsuka Pharmaceutical Development & Commercialization, Inc.
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Keywords: Clinical studies, NDA review, One study application, Pediatric exclusivity

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results of study 31-03-240 showed that aripiprazole 10 mg/day and 30 mg/day were effective in the treatment of bipolar I disorder, manic or mixed episode in children and adolescents ages 10 to 17, as measured by the change from baseline to Week 4 in the Young Mania Rating Scale (YMRS) total score.

1.2 Brief Overview of Clinical Studies

Study 31-03-240 was a United States (U.S.) multi-center, randomized, double-blind, placebo-controlled study designed to fulfill the U.S. Food and Drug Administration (FDA) pediatric written request. The study consisted of a 4-week acute phase followed by a 26-week extension phase. Two fixed doses of aripiprazole (10 mg/day and 30 mg/day) were compared to placebo in adolescent subjects, ages 10 to 17, with bipolar I disorder, manic or mixed episode. Patients were titrated to the target dose. The primary endpoint in the acute phase was the change from baseline to Week 4 in the Young Mania Rating Scale (YMRS) total score.

For the United States registration, only the acute phase is required. In addition, due to a high dropout rate in the extension phase, this review focuses on the acute phase only.

1.3 Statistical Issues and Findings

Both doses of aripiprazole were superior to placebo in the change from baseline to Week 4 in the YMRS total score.

2. INTRODUCTION

2.1 Overview

This document contains a statistical evaluation of aripiprazole as an acute treatment for adolescent patients with bipolar I disorder.

According to the sponsor, bipolar I disorder is a lifelong episodic illness characterized by manic or depressive episodes followed by symptom-free periods. The estimated prevalence of bipolar disorder is 0.4% to 1.6%.

Aripiprazole is currently indicated in the United States for the treatment in adults with acute schizophrenia, maintenance of stability in schizophrenia, treatment of acute manic and mixed episodes associated with bipolar disorder, and for maintaining efficacy in adult patients with bipolar I disorder. In this application, the sponsor submitted one multi-center, randomized, double-blind, placebo-controlled, parallel group study (Study 31-03-240) in response to the U.S. Food and Drug Administration (FDA) pediatric written request. The purpose of the study is to demonstrate the efficacy and safety of aripiprazole as an acute treatment of bipolar I disorder in adolescents ages 10 to 17 years.

Study 31-03-240 was a United States multi-center study that had two phases. An acute phase lasted four weeks. Patients reached Week 4 continued into an extension phase that lasted for an additional 26 weeks.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room:
\\Cdsesub1\nonectd\N21436\S_021\2007-08-28\crt\datasets

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Objectives

The primary objectives of the study were to compare the efficacy of two fixed doses of aripiprazole (10 mg and 30 mg) to placebo, and to assess the safety of aripiprazole in child and adolescent patients, ages 10-17 years, with bipolar I disorder, manic or mixed episode with or without psychotic features.

3.1.2 Study Design

Study 31-03-240 was a United States, multi-center, randomized, double-blind, placebo-controlled study. The study consisted of three phases: a screening phase, an acute phase, and an extension phase. Subjects were screened for a period up to 28 days (including appropriate medication washout), and if they met entrance criteria, they were randomized to either 10 mg or 30 mg of aripiprazole or placebo. In the acute treatment phase, randomized patients received treatment for a period of four weeks. If the subjects reached Week 4, they would continue into the extension phase, an additional 6-month double-blind treatment period. In order to ensure that only eligible subjects were enrolled in the study, the DSM-IV diagnosis of subjects with bipolar I disorder were carried out by an experienced clinician who was adequately trained in child and adolescent psychiatry. Subjects had to have an YMRS total score of at least 20 at baseline to be eligible. Patients received treatment according to the following titration schedule:

Table 1. Titration schedule

Days	1-2	3-4	5-6	7-8	9-10	11-12	13-28
10 mg arm	2 mg	5 mg	10 mg	10 mg	10 mg	10 mg	10 mg
30 mg arm	2 mg	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Placebo arm	Matching Placebo						

Patients reached Week 4 could continue into a 26-week double-blind extension phase. The dose in the extension phase was the same dose taken during the acute phase. The investigator had the option to down-titrate a subject's dose only one time during the extension phase to half of the target dose for tolerability reasons. Following the down-titration, the investigator could also up-titrate one time as needed to enhance efficacy.

The study was designed to have 85% power to detect a difference of 5.1 points (standard deviation 11.1 points) for the change from baseline in YMRS total score at week 4.

3.1.3 Efficacy Endpoint and Analysis

Primary endpoint and analysis: The primary efficacy endpoint was the change from baseline in YMRS total score at Week 4 with missing value imputed by the last observation carried forward (LOCF) method. The primary statistical comparisons were aripiprazole 10 mg dose versus placebo, and aripiprazole 30 mg dose versus placebo. The primary analysis model was an analysis of covariance (ANCOVA) model with treatment as a factor and baseline YMRS total score as a covariate. To account for multiple comparisons, an overall F-test was performed to test the hypothesis that the mean changes of the three treatment groups were equal. If this hypothesis was rejected at a 0.05 level, then each of the aripiprazole groups were compared to placebo at a 0.05 level. Assessments of the primary endpoint for the acute phase were done on

screening, baseline, Day 4 (phone call), Weeks 1, 2, 3, and 4, or early discontinuation.

The sponsor did not declare any key secondary endpoint.

3.1.4 Efficacy Results

3.1.4.1 Study Population

Between March 2005 and February 2007, 296 subjects were randomized. About 80% of the participants completed the acute phase. The completion rates were higher for the two aripiprazole groups than the placebo group. Reasons for dropping out included consent withdrawals, lack of efficacy, adverse events, and lost to follow-up. There were more subjects dropping out in the placebo arm due to lack of efficacy. On the contrary, more subjects dropped out of the aripiprazole groups due to adverse events. Table 2 captures the subject disposition.

Table 2. Subject disposition

	Aripi 10mg	Aripi 30mg	Placebo	Total
Randomized: n (%)	98 (100)	99 (100)	99 (100)	296 (100)
Withdrawn: n (%)	14 (14.3)	22 (9.1)	23 (34.8)	59 (19.9)
Lost to follow-up	3 (3.1)	3 (3.0)	5 (5.1)	11 (3.7)
Adverse events	4 (4.1)	7 (7.1)	1 (1.0)	12 (4.1)
Investigator withdrew consent	1 (1.0)	0 (0.0)	2 (2.0)	3 (1.0)
Subject withdrew Consent	4 (4.1)	9 (9.1)	6 (6.1)	19 (6.4)
Protocol deviation	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.7)
Lack of efficacy	2 (2.0)	2 (2.0)	8 (8.1)	12 (4.1)
Completers: n (%)	84 (85.7)	77 (77.8)	76 (76.8)	237 (80.1)
Efficacy set: n	96	99	92	287

(Source: 31-03-240 Study Report: Tables 8.1-1 page 108)

Roughly 50% of subjects in the randomized sample were male. The average age was 13.4 years and ranged from 10 to 17 years. Most subjects were Caucasian (65%) and African American (22%). The baseline body mass index (BMI) and YMRS total score were relatively similar for aripiprazole groups and placebo group. Table 3 summarizes demographic and baseline disease characteristics in the randomized sample.

Table 3. Demographic and baseline characteristics (randomized sample)

	Aripi 10mg (N = 98)	Aripi 30mg (N = 99)	Placebo (N = 99)	Total (N = 296)
Male: n (%)	52 (53.1)	51 (51.5)	56 (56.6)	159 (53.7)
Age (*)				
Mean (SD)	13.7 (2.2)	13.3 (2.3)	13.3 (2.1)	13.4 (2.2)
Range	10 – 17	10 – 17	10 – 17	10 – 17
Race: n (%)				
Caucasian	65 (66.3)	68 (68.7)	60 (60.6)	193 (65.2)
Black	24 (24.5)	18 (18.2)	23 (23.2)	65 (22.0)
Native Hawaiian / Pacific Islander	2 (2.0)	0 (0.0)	(0.0)	2 (0.7)
Other	7 (7.1)	13 (13.1)	16 (16.2)	36 (12.2)
BMI (*)				
Mean (SD)	24.1 (5.4)	23.7 (6.7)	23.7 (5.0)	23.8 (5.7)
Range	14.2 – 42.0	12.7 – 43.7	14.4 – 34.9	12.7 – 43.7
YMRS (*)				
Mean (SD)	29.8 (6.4)	29.5 (6.3)	30.7 (6.8)	30.0 (6.5)
Range	20 – 45	20 – 46	16 – 50	16 – 50

(*) Characteristics at baseline
(Source: 31-03-240 Study Report: Tables 8.2-1 and 8.2-2, pages 109 and 110)

3.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy endpoint was the mean change from baseline to Week 4 in YMRS total score. Missing values were imputed by the last-observation-carried-forward (LOCF) method. The primary analysis model was ANCOVA with baseline YMRS total score as a covariate and treatment as a factor. Table 4 presents the sponsor's primary analysis results. Since the overall F test was significant, indicating there was a difference among the three treatment arms, both aripiprazole 10 mg and 30 mg groups were compared to placebo. Both aripiprazole groups were statistically significantly better than placebo in lowering the YMRS total score from baseline to Week 4.

Table 4. Primary efficacy analysis: YMRS total score, change from baseline to Week 4 (LOCF)

	Aripi 10mg	Aripi 30mg	Placebo
Sample size (N)	96	99	92
P-value (overall F Test)	<0.0001		
LS Means	-14.2	-16.5	-8.2
Difference from placebo (95% CI)	-5.99 (-8.49, -3.50)	-8.26 (-10.74, -5.77)	
P-value	<0.0001	<0.0001	

(Source: 31-03-240 Study Report: Table 9.3.1-1, page 114)

3.1.4.3 Sponsor's Other Efficacy Results

Primary endpoint based on an ANCOVA model on observed cases (OC): Table 5 presents an ANCOVA analysis of the primary endpoint based on observed cases. The ANCOVA model included baseline YMRS total score as a covariate and treatment as a factor. The results were consistent with the primary analysis.

Table 5. Primary endpoint analysis: YMRS total score, change from baseline to Week 4 (OC)

	Aripi 10mg	Aripi 30mg	Placebo
Sample size (N)	78	75	67
P-value (overall F Test)	<0.0001		
LS Means	-15.0	-17.1	-9.2
Difference from placebo (95% CI)	-5.81 (-8.51, -3.12)	-7.92 (-10.63, -5.20)	
P-value	<0.0001	<0.0001	

(Source: 31-03-240 Study Report: Table 9.3.1-1, page 114)

Primary endpoint analyses over time (LOCF):
Analyses of the YMRS total score, change from baseline to each visit in the acute phase are presented in Table 6. Observed improvements were seen as early as Week 1 for both dose groups and continued through Week 4.

Table 6. Primary endpoint analysis: YMRS total score, change from baseline to Week 1-4 (LOCF)

Week	Aripi 10 mg N	Aripi 10 mg LS Mean	Aripi 30 mg N	Aripi 30 mg LS Mean	Placebo N	Placebo LS Mean	Difference (P-value*) Aripi 10 mg vs. placebo	Difference (P-value*) Aripi 30 mg vs. placebo
Week 1	92	-9.0	95	-9.4	87	-5.6	-3.4 (0.0023)	-3.8 (0.0006)
Week 2	94	-12.8	99	-13.7	92	-7.7	-5.1 (<.0001)	-6.0 (<.0001)
Week 3	96	-13.9	99	-15.0	92	-8.1	-5.8 (<.0001)	-6.9 (<.0001)
Week 4	96	-14.2	99	-16.5	92	-8.2	-6.0 (<.0001)	-8.3 (<.0001)

(Source: 31-03-240 Study Report: Table 9.3.1-1, page 114 and reviewer's results)
*Reviewer's note: P-values are not adjusted for multiple comparisons

3.1.4.4 Statistical Reviewer's Results and Comments
This reviewer confirmed the findings for the primary endpoint as presented in Table 4.

There appears no additional benefit of aripiprazole 30 mg over 10 mg. The difference between the two aripiprazole dose groups was -2.3 points in YMRS total score in favor of the 30 mg dose. However, the difference appeared not statistically significant.

This reviewer also performed an analysis based on the mixed effect models for repeated measures (MMRM). The model included the change from baseline to each post baseline visit in YMRS total score as a dependent variable; baseline YMRS total score as a covariate; treatment group, and visit week as fixed effect factors; and a treatment-by-visit fixed effect interaction. The within subject covariance matrix was unstructured. The method of estimation was restricted maximum likelihood (ReML). The denominator degrees of freedom were approximated using the Satterthwaite approach. The results are presented in Table 7 and are supportive of the primary analysis.

Table 7. Primary endpoint analysis: YMRS total score, change from baseline to Week 4 (MMRM)

	Aripi 10mg	Aripi 30mg	Placebo
LS Means	-14.7	-17.4	-8.8
Difference from placebo (95% CI)	-5.86 (-8.46, -3.27)	-8.56 (-11.17, -5.95)	
P-value	<0.0001	<0.0001	

(Source: Reviewer's results)

3.2 Evaluation of Safety

Please refer to the clinical review for safety evaluation and report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Gender

The primary efficacy analyses stratified by gender are presented below. Both groups showed numerical improvements over placebo. The magnitude of difference appeared higher for males than females.

Table 8. Primary efficacy analysis by gender: YMRS total score, change from baseline to Week 4 (LOCF)

	Aripi 10mg	Aripi 30mg	Placebo
Male			
Sample size	50	51	51
LS Means	-15.0	-17.1	-7.5
Difference from placebo (95% CI)	-7.6 (-11.0, -4.1)	-9.7 (-13.1, -6.2)	
Female			
Sample size	46	48	41
LS Means	-13.3	-15.7	-9.2
Difference from placebo (95% CI)	-4.1 (-7.8, -0.4)	-6.6 (-10.2, -2.9)	

(Source: Reviewer's results)

4.1.2 Race

Table 9 presents the primary efficacy analyses by race. Numerical improvements were seen in all three race groups. However, due to small sample sizes in the African American and other race groups, the results should be interpreted with caution.

Table 9. Primary efficacy analysis race: YMRS total score, change from baseline to Week 4 (LOCF)

	Aripi 10mg	Aripi 30mg	Placebo
Caucasian			
Sample size	63	68	58
LS Means	-14.8	-16.7	-6.5
Difference from placebo (95% CI)	-8.3 (-11.3, -5.2)	-10.2 (-13.2, -7.2)	
African American			
Sample size	24	18	20
LS Means	-12.3	-17.0	-9.4
Difference from placebo (95% CI)	-2.9 (-8.0, 2.2)	-7.6 (-13.1, -2.1)	
Others			
Sample size	9	13	14
LS Means	-14.9	-15.0	-13.4
Difference from placebo (95% CI)	-1.6 (-9.8, 6.7)	-1.6 (-9.1, 5.9)	

(Source: Reviewer's results)

4.1.3 Age

Subjects in this study were children and adolescents between the ages of 10 to 17. The primary analyses stratified by age are presented below. The magnitude of the effect appeared larger among patients ages 10 to 13 than among patients ages 14 to 17.

Table 10. Primary efficacy analysis by age: YMRS total score, change from baseline to Week 4 (LOCF)

	Aripi 10mg	Aripi 30mg	Placebo
Ages 10 - 13			
Sample size	43	54	51
LS Means	-14.2	-15.9	-6.0
Difference from placebo (95% CI)	-8.2 (-11.6, -4.8)	-9.9 (-13.1, -6.6)	
Ages 14 - 17			
Sample size	53	45	41
LS Means	-14.5	-17.0	-10.8
Difference from placebo (95% CI)	-3.6 (-7.3, 0.0)	-6.2 (-9.9, -2.4)	

(Source: Reviewer's results)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Both doses of aripiprazole were superior to placebo in the change from baseline to Week 4 in the YMRS total score.

5.2 Conclusions and Recommendations

The results of study 31-03-240 showed that aripiprazole 10 mg/day and 30 mg/day were effective in the treatment of bipolar I disorder, manic or mixed episode in children and adolescents ages 10 to 17, as measured by the change from baseline to Week 4 in the Young Mania Rating Scale (YMRS) total score.

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