DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-436/S017
Drug Name:	Abilify® (Aripiprazole)
Indication:	Treatment of Adolescent Patients with Schizophrenia
Applicant:	Otsuka Pharmaceutical
Dates:	Date of Document: 03/23/2007
	PDUFA Due Date: 09/27/2007
Review Priority:	Priority
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.
	Kooros Mahjoob, Ph.D.
Medical Division:	Division of Psychiatry Products, HFD-130
Clinical Team:	Clinical Reviewer: Jing Zhang, M.D.
	Clinical Team Leader: Mitchell Mathis, M.D. (Deputy Director and also Acting Team Leader)
Project Manager:	Keith Kiedrow, Pharm. D., LCDR USPHS

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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The only submitted efficacy study 31-03-239 is determined to be a positive study, which demonstrated the aripiprazole's efficacy (both 10 mg/day and 30 mg/day) for the treatment of adolescent schizophrenia. Now that 10 mg/day of aripiprazole had shown statistically significant efficacy. (b) (4)

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submitted Study 31-03-239 as part of the Abilify™ (aripiprazole) pediatric efficacy program designed to address the FDA's Written Request to systematically study the safety and efficacy of aripiprazole in adolescents aged 13 to 17 years with schizophrenia. This study tested the safety and efficacy of aripiprazole tablets 10 mg/day and 30/day compared to placebo in adolescent patients with schizophrenia. Based on the sponsor's analysis results for the primary endpoint, change from baseline to Week 6 (LOCF data) in the PANSS Total Score, they concluded that aripiprazole was effective in the treatment of adolescent subjects with schizophrenia at daily doses of 10 mg and 30 mg. (b) (4)

1.3 STATISTICAL ISSUES AND FINDINGS

This reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints for Study 31-03-239. It was agreed that the aripiprazole's efficacy at both 10 mg/day and 30 mg/day for adolescent schizophrenia patients was demonstrated based on this only efficacy study (b) (4)

Now that the 10 mg/day of aripiprazole had already been shown to have statistically significant efficacy in comparison with placebo as a treatment of adolescent schizophrenia, (b) (4)

2. INTRODUCTION

This study 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.

2.1 OVERVIEW

Abilify® (aripiprazole, OPC-14597, BMS-337039) is approved in the United States of America 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 of bipolar disorder (as of September 2004), and for the maintenance of efficacy in bipolar I disorder (as of March 2005). 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), one randomized, double-blind, placebo-controlled safety and efficacy study each in schizophrenia subjects and bipolar mania subjects (Studies 31-03-239 and 31-03-240), and a roll-over, open-label safety study for subjects who complete either of the double-blind trials (31-03-241).

The efficacy study included in this NDA submission is Study 31-03-239 for the adolescent subjects (aged 13 to 17 years) with schizophrenia. Based on the study results, the sponsor concluded that aripiprazole was effective at daily doses of 10 mg and 30 mg. The primary efficacy measure used in the trial was the mean change from Baseline to Endpoint (Day 42) in the Positive and Negative Syndrome Scale (PANSS) Total Score.

2.2 DATA SOURCES

This NDA submission including the data and study report are stored in the EDR of CDER with the following link: \\CDSESUB1\N21436\S_017\2007-03-23.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Description of Study 31-03-239

This section of study description is based on the clinical study report (CSR) in the NDA submission. Any major discrepancy between this CSR and the study protocol will be discussed in the section of the statistical reviewer's findings and comments.

3.1.1.1 Study Objectives

The primary objective of this study was to determine the safety and efficacy of aripiprazole tablets administered as 10 mg QD and 30 mg QD in adolescent subjects, 13 to 17 years of age, with a DSM-IV diagnosis of schizophrenia. This study was designed in response to the FDA's PWR.

3.1.1.2 Study Design

This study was a multi-center, 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 subjects, 13 to 17 years of age (inclusive), with a DSM-IV diagnosis of schizophrenia. The DSM-IV diagnosis was confirmed by administering the Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version (K-SADS-PL) semi-structured interview of patients and parents/caregivers by an adequately trained clinician. Confirmation of the DSM-IV diagnosis of schizophrenia using a valid and reliable semi-structured interview was required in the PWR. These procedures could have been completed over multiple clinic visits if necessary.

The study was conducted on an outpatient basis (with the option for inpatient hospitalization, if needed), and in a partial or full inpatient setting at any given time in the study. A minimum of 350 subjects at approximately 141 sites globally were anticipated to be screened with the expectation that approximately 300 subjects would be randomized to yield at least 255 evaluable subjects (85 per treatment arm). Subjects participated in this study for up to 10 weeks, including a 28-day screening period, and a 42-day treatment period. Eligible subjects who completed this study had the option to enroll into an open-label safety study of aripiprazole (Study 31-03-241) for an additional 6 months.

After a minimum 3-day antipsychotic washout period, only subjects who continued to meet entrance criteria (PANSS≥70) at the baseline visit (Day 1) were evenly randomized to receive a double-blind medication as follows:

- Arm 1 (10 mg treatment arm): Aripiprazole 2 mg QD for 2 days, aripiprazole 5 mg QD for 2 days, and aripiprazole 10 mg QD as the target dose, starting on Day 5.
- Arm 2 (30 mg treatment arm): Aripiprzole 2 mg QD for 2 days, aripiprazole 5 mg AD for 2 days, aripiprazole 10 mg QD for 2 days, aripiprazole 15 mg AD for 2 days, aripiprazole 20 mg QD for 2 days, aripiprazole 30 mg QD as the target dose, starting on Day 11.
- Arm 3 (placebo arm): Matching placebo for aripiprazole tablets.

3.1.1.3 Efficacy Variables and Analyses

Efficacy Variables

The primary efficacy measure was the mean change from baseline to endpoint (Day 42) in the Positive and Negative Syndrome Scale (PANSS) Total Score. Secondary efficacy measures include mean changes in scores from baseline to endpoint (Day 42) in the Children's Global Assessment Scale (CGAS), CGI-Severity, CGI-Improvement, and PANSS Positive and PANSS Negative Subscales; and time to discontinuation due to all reasons.

Efficacy Analyses

The null hypothesis for the primary efficacy analysis in this study is that there is no difference between either of the two aripiprazole treatment groups and the placebo control group based on change from baseline in the PANSS Total Score. The primary efficacy endpoint was the change from baseline in PANSS Total Score at Day 42 (Week 6) in the LOCF data set. The primary statistical comparisons were aripiprazole 10-mg target dose versus placebo, and aripiprazole 30-mg target dose versus placebo. All randomized subjects who had both baseline and post-baseline PANSS Total Score were included in the primary efficacy analysis.

Descriptive statistics for PANSS Total Scores and change from baseline scores were presented by treatment group for each visit. The change from baseline scores (LOCF) were analyzed using an analysis of covariance (ANCOVA) model with treatment and region as factors, and baseline PANSS Total Score as covariate. The treatment by region interaction term was investigated. For the baseline PANSS Total Score, only treatment and region were included in the analysis of variance (ANOVA) model. The least squares (LS) means obtained from the type III analysis using Statistical Analysis System were used for the treatment comparisons. Two-tailed student's t-tests were used to test the difference between LS means within the ANCOVA or ANOVA model.

A nominal overall significance level of 0.05 (two-tailed) was used in testing statistical significance of these two comparisons. In order to account for multiplicity in testing the two comparisons, the following Hochberg's procedure was used: if both p-values were less than 0.05 (two-tailed), statistical significance was declared for both doses. If the larger of the two p-values was greater than 0.05, the smaller p-value was compared with 0.025 (two-tailed) and the corresponding treatment comparison was declared statistically significant if this p-value was less than 0.025.

In addition to the primary analysis of the PANSS Total Score at Week 6, analyses of changes from baseline in PANSS Total Scores were performed as secondary analyses at all scheduled visits for both LOCF and OC data sets.

3.1.2 Efficacy Results of Study 31-03-239

3.1.2.1 Disposition of Patients and Baseline Characteristics

The subject disposition was summarized in Table 1. Of the 302 subjects enrolled, all were analyzed for efficacy and safety. Demographic characteristics are summarized in Table 2. The three treatment arms were demographically similar and had similar baseline disease characteristics. The majority of subjects were male (56.6%), Caucasian (60.0%), and non-Hispanic (86.0%). The mean age was 15.5 years (range, 13.0 to 17.0 years).

Table 1 Subject Disposition for Study 31-03-239

	ARIP-10 mg	ARIP-30 mg	Placebo	Total
Screened				371
Randomized	100 (100)	102 (100)	100 (100)	302 (100)
Dosed/Analyzed for Safety	100 (100)	102 (100)	100 (100)	302 (100)
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)
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 as determined by the investigator	5 (5.0)	1 (1.0)	1 (1.0)	7 (2.3)
Analyzed for Efficacy	100 (100)	102 (100)	100 (100)	302 (100)

Source: Sponsor's Table 8.1-1 of Clinical Study Report

Table 2 Demographic Characteristics for All Randomized Subjects for Study 31-03-239

Characteristic	Statistic	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)
	Range	13-17	13-17	13-17	13-17
Height (cm)	N	100	102	100	302
	Mean (SD)	164.0 (10.8)	167.1 (11.4)	166.0 (10.0)	165.7 (10.8)
	Range	139.0-191.0	140.8-196.5	141.0-198.0	139.0-198.0
Weight (kg)	N	100	102	100	302
	Mean (SD)	63.5 (19.1)	64.5 (16.0)	63.4 (15.6)	63.8 (16.9)
	Range	30.0-131.0	36.0-124.5	36.7-108.0	30.0-131.0
BMI	N	100	102	100	302
	Mean (SD)	23.5 (6.0)	23.0 (4.9)	22.9 (5.3)	23.1 (5.4)
	Range	13.6-51.1	16.1-43.0	15.3-40.3	13.6-51.1
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)
	American Indian or Alaskan Native, n (%)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
	Asian, n (%)	16 (16.0)	12 (12.0)	15 (15.0)	43 (14.0)
	Other, n (%)	13 (13.0)	17 (17.0)	14 (14.0)	44 (15.0)
Ethnicity	Hispanic/Latino, n (%)	12 (12.0)	15 (15.0)	14 (14.0)	41 (14.0)
	NonHispanic/Latino, n (%)	88 (88.0)	87 (85.0)	86 (86.0)	261 (86.0)

Source: Sponsor's Table 8.2-1 of Clinical Study Report

3.1.2.2 Sponsor's Efficacy Analysis Results

Primary Endpoint

The sponsor's analysis results for the mean change from baseline in PANSS Total Score by week are presented in the following Table 3. As shown in the table, 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 aripirpazole 10 mg versus placebo and p=0.0061 for aripiprazole 30 mg versus placebo).

Using the OC data set, the PANSS Total Score 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 ariprazole 10 mg versus placebo and p = 0.0002 for aripiprazole 30 mg versus placebo). The detailed weekly OC analysis results are shown in Table 6.1 of Appendix.

Table 3 Sponsor's Analysis Results for Mean Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score by Week (LOCF) for Study 31-03-239

Visit/Week	Arip 10 mg		Arip 30 mg		Placebo		P-value Arip10 mg vs. Placebo	P-value Arip 30 mg vs. Placebo
	N	Mean*	N	Mean*	N	Mean*		
Baseline	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	99	-26.7	97	-28.6	98	-21.2	0.0414	0.0061

* The reported means are least square means adjusted from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata.
Source: Sponsor's Table 9.3.1-1 of Clinical Study Report

Reviewer's Note: There were 8 patients who were randomized but did not have any post randomization PANSS Total Score, so only total 294 patients were included in the primary analysis results.

Secondary Endpoints

Table 4 summarized the sponsor's analysis results for CGAS Score, CGI-Severity Score, CGI Improvement Score, PANSS Positive Subscale Score, PANSS Negative Subscale Score. Regarding the time to discontinuation for all reasons variable, the sponsor showed a Kaplan-Meier product limit plot and concluded that no statistically significant differences were observed between the aripiprazole 10 mg arm and placebo or the aripiprazole 30 mg arm and placebo.

Table 4 Summary of Sponsor's Analysis Results for Secondary Endpoints

Visit/Week	Arip 10 mg		Arip 30 mg		Placebo		P-value Arip10 mg vs. Placebo	P-value Arip 30 mg vs. Placebo
	N	Mean*	N	Mean*	N	Mean*		
Mean Change from Baseline to Week 6 in CGAS Score (LOCF)								
Baseline	97	46.7	94	45.6	98	45.4	0.4278	0.8667
Week 6	97	14.7	94	14.8	98	9.8	0.0054	0.0044
Mean Change from Baseline to Week 6 in CGI Severity Score (LOCF)								
Baseline	99	4.5	97	4.6	98	4.6	0.2381	0.5990
Week 6	99	-1.2	97	-1.3	98	-0.9	0.0071	0.0016
Mean CGI Improvement Score (LOCF)								
Week 6	99	2.7	97	2.5	98	3.1	0.0167	0.0004
Mean Change from Baseline to Week 6 in PANSS Positive Subscale Score (LOCF)								
Baseline	99	22.1	97	23.5	98	22.9	0.2548	0.4602
Week 6	99	-7.6	97	-8.1	98	-5.6	0.0134	0.0018
Mean Change from Baseline to Week 6 in PANSS Negative Subscale Score (LOCF)								
Baseline	99	25.4	97	24.9	98	25.6	0.7881	0.3984
Week 6	99	-6.9	97	-6.6	98	-5.4	0.0462	0.0972

Source: Sponsor's Tables 9.4.2-1 to 9.4.6-1 of Clinical Study Report

3.1.2.3 Reviewer's Findings and Comments

This reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints for Study 31-03-239. It was agreed that the aripiprazole's efficacy at both 10 mg/day and 30 mg/day for adolescent schizophrenia patients was demonstrated based on this only efficacy study. This reviewer also noted that the sponsor claimed (b) (4) [redacted] Now that the 10 mg/day of aripiprazole had already shown statistically significant efficacy in comparison with placebo as a treatment of adolescent schizophrenia, (b) (4) [redacted]

3.2 EVALUATION OF SAFETY

Please refer to the medical review for the evaluation of safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

For the primary endpoint, the sponsor performed the subgroup analyses for region, gender, and race for Study 31-03-239. Since this study was only the aripiprazole's efficacy in the treatment of adolescent patients, which were aged from 13 to 17 years, no age subgroup analysis was performed. This reviewer confirmed the sponsor's analysis results. For exploratory purpose, this reviewer also performed the ANCOVA analyses by including the factor of treatment and a covariate of baseline PANSS Total scores.

4.1 GENDER, RACE AND AGE

The sponsor's subgroup analyses for gender and race are shown in Tables 5 and 6. 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.

Table 5 Sponsor's Gender Subgroup Analysis Results for Change from Baseline to End Visit of PANSS Total Score (by LOCF Data) for Study 31-03-239

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
Male			
Arip-10 mg (N=44)	Baseline	94.5 (14.3)	-27.1 (19.0)
	Last Visit (Week 6)	67.4 (20.6)	
Arip-30 mg (N=61)	Baseline	95.0 (13.5)	-27.9 (20.2)*
	Last Visit (Week 6)	67.0 (19.5)	
Placebo (N=59)	Baseline	94.6 (16.7)	-20.2 (19.3)
	Last Visit (Week 6)	74.4 (22.2)	
Female			
Arip-10 mg (N=55)	Baseline	93.1 (16.9)	-24.1 (21.4)
	Last Visit (Week 6)	69.0 (25.0)	
Arip-30 mg (N=36)	Baseline	94.9 (18.6)	-27.5 (20.0)
	Last Visit (Week 6)	67.4 (25.3)	
Placebo (N=39)	Baseline	95.6 (13.5)	-20.2 (16.5)
	Last Visit (Week 6)	75.4 (17.8)	

*: 0.01<p-value<0.05 by the ANCOVA model with treatment and baseline.
Source: Sponsor's Table STAT-1.1.1.3

Table 6 Sponsor's Race Subgroup Analysis Results for Change from Baseline to End Visit of PANSS Total Score (by LOCF Data) for Study 31-03-239

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
White			
Arip-10 mg (N=53)	Baseline	92.3 (16.4)	-21.5 (19.7)
	Last Visit (Week 6)	70.8 (21.5)	
Arip-30 mg (N=59)	Baseline	92.2 (14.2)	-24.2 (21.0)*
	Last Visit (Week 6)	68.0 (20.2)	
Placebo (N=64)	Baseline	92.2 (13.2)	-17.0 (16.8)
	Last Visit (Week 6)	75.1 (17.9)	
Black or African American			
Arip-10 mg (N=17)	Baseline	95.6 (17.8)	-32.8 (20.3)
	Last Visit (Week 6)	62.8 (22.8)	
Arip-30 mg (N=11)	Baseline	105.6 (13.4)	-24.2 (12.9)
	Last Visit (Week 6)	81.5 (19.9)	
Placebo (N=6)	Baseline	98.5 (16.7)	-35.3 (26.0)
	Last Visit (Week 6)	63.2 (23.8)	

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
American Indian or Alaska Native			
Placebo (N=1)	Baseline	98.0	-17.0
	Last Visit (Week 6)	81.0	
Asian			
Arip-10 mg (N=16)	Baseline	91.3 (11.5)	-23.1 (21.0)
	Last Visit (Week 6)	68.2 (29.3)	
Arip-30 mg (N=12)	Baseline	90.3 (11.0)	-39.3 (15.7)
	Last Visit (Week 6)	51.1 (13.8)	
Placebo (N=13)	Baseline	97.2 (15.8)	-25.2 (19.1)
	Last Visit (Week 6)	72.1 (22.4)	
Other			
Arip-10 mg (N=13)	Baseline	99.8 (14.4)	-34.7 (18.9)
	Last Visit (Week 6)	65.2 (22.6)	
Arip-30 mg (N=15)	Baseline	101.5 (20.3)	-35.2 (19.6)
	Last Visit (Week 6)	66.3 (26.7)	
Placebo (N=14)	Baseline	104.1 (21.6)	-23.6 (17.2)
	Last Visit (Week 6)	80.5 (28.1)	

*: 0.01<p-value<0.05 by the ANCOVA model with treatment and baseline.
Source: Sponsor's Table STAT-1.1.1.4

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Table 7 shows the sponsor's results of subgroup analysis by region. This reviewer found that all comparisons between aripiprazole (15 mg or 30 mg) and placebo had nominal p-values >0.05.

Table 7 Sponsor's Region Subgroup Analysis Results for Change from Baseline to End Visit of PANSS Total Score (by LOCF Data) for Study 31-03-239

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
US			
Arip-10 mg (N=31)	Baseline	97.2 (16.5)	-31.4 (22.5)
	Last Visit (Week 6)	65.8 (21.8)	
Arip-30 mg (N=31)	Baseline	101.3 (15.1)	-30.7 (21.4)
	Last Visit (Week 6)	70.5 (24.1)	
Placebo (N=31)	Baseline	98.6 (17.0)	-23.7 (20.9)
	Last Visit (Week 6)	74.9 (26.8)	
Europe			
Arip-10 mg (N=17)	Baseline	92.2 (16.1)	-21.8 (19.3)
	Last Visit (Week 6)	70.4 (22.1)	
Arip-30 mg (N=11)	Baseline	88.5 (11.9)	-21.2 (16.2)
	Last Visit (Week 6)	67.3 (16.6)	
Placebo (N=6)	Baseline	91.9 (12.7)	-15.8 (16.1)
	Last Visit (Week 6)	76.1 (15.4)	

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
Other Regions			
Arip-10 mg (N=17)	Baseline	92.0 (13.7)	-24.6 (18.1)
	Last Visit (Week 6)	67.4 (27.2)	
Arip-30 mg (N=11)	Baseline	99.0 (17.9)	-36.7 (21.5)
	Last Visit (Week 6)	62.4 (26.8)	
Placebo (N=6)	Baseline	96.7 (18.1)	-25.1 (16.4)
	Last Visit (Week 6)	71.6 (20.5)	

Source: Sponsor's Table STAT-1.1.1.2

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

This reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints for Study 31-03-239. It was agreed that the aripiprazole's efficacy at both 10 mg/day and 30 mg/day for adolescent schizophrenia patients was demonstrated based on this only efficacy study (b) (4)

5.2 CONCLUSIONS AND RECOMMENDATIONS

The only submitted efficacy study 31-03-239 is determined to be a positive study, which demonstrated the aripiprazole's efficacy (both 10 mg/day and 30 mg/day) for the treatment of adolescent schizophrenia. Now that 10 mg/day of aripiprazole had shown statistically significant efficacy, (b) (4)

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 21-436 (S17)
HFD-130/Dr. Laughren
HFD-130/Dr. Mathis
HFD-130/Dr. Zhang
HFD-130/Mr. Kiedrow
HFD-700/Dr. Nevius
HFD-700/Ms. Patrician
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Yang

6. APPENDICES

Table 6.1 Sponsor's OC analysis Results for PANSS Total Score for Study 31-03-239

Visit/Week	Arip 10 mg		Arip 30 mg		Placebo		P-value Arip10 mg v.s. Placebo	P-value Arip 30 mg v.s. Placebo
	N	Mean*	N	Mean*	N	Mean*		
Baseline	99	93.7	97	94.9	98	95.0	0.54	0.94
Week 1	98	-6.9	95	-10.4	97	-7.2	0.84	0.05
Week 2	97	-14.0	93	-15.7	95	-12.3	0.4	0.11
Week 3	88	-20.1	90	-23.4	93	-17.9	0.35	0.02
Week 4	87	-24.0	85	-26.4	91	-19.3	0.03	0.002
Week 5	86	-27.6	84	-30.4	88	-21.7	0.01	0.0003
Week 6	84	-30.6	84	-31.9	90	-22.3	0.0011	0.0002

* The reported means are least square means. Source: Sponsor's Table CT-5.1.2.

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