CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202-971/S003

STATISTICAL REVIEW(S)

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/Supplement Number (Serial Number):	202971/S-3 (S0055)
Drug Name:	Abilify Maintena™ (aripiprazole extended-release injectable suspension)
Indication:	Schizophrenia
Applicant:	Otsuka
Dates:	Date of Document: February 7, 2014 PDUFA Due Date: December 7, 2014
Review Priority:	Standard
Biometrics Division:	Biometrics I
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
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1. EXECUTIVE SUMMARY

The sponsor submitted a single phase 3 trial to demonstrate the efficacy of ABILIFY® MAINTENA™ (aripiprazole), an extended-release injectable suspension for once-monthly IM use, as (b) (4) treatment of schizophrenia. After evaluation, the statistical reviewer agreed with the sponsor's efficacy findings at Week 10 based on the PANSS total score and the CGI-S score (b) (4)

2. INTRODUCTION

2.1 OVERVIEW

In 2012, aripiprazole (ABILIFY®), a dopamine partial agonist discovered by Otsuka Pharmaceutical Company (OPC) and co-developed with Bristol-Myers Squibb, was approved as a treatment of schizophrenia in oral use in the United States. In 2013, ABILIFY® MAINTENA™ (aripiprazole), an extended-release injectable suspension for once-monthly IM use, was approved as a treatment of schizophrenia but for the maintenance treatment of schizophrenia based on data of two long-term maintenance trials. In this supplemental new drug application (sNDA), the sponsor primarily included a single short term efficacy Trial 31-12-291 to support the use of aripiprazole IM depot for treatment (b) (4) of schizophrenia. They also included safety data for Trial 31-12-297, which was an ongoing open-label extension trial enrolling only subjects who completed Trial 31-12-291.

Trial 31-12-291 used a 12-week randomized, double-blind, placebo-controlled design to evaluate the efficacy, safety, and tolerability of aripiprazole IM depot. The primary efficacy endpoint was the change from baseline to **Week 10** in the PANSS total score analyzed by the MMRM method and the key secondary efficacy endpoint was the change from baseline to Week 10 in the CGI-S score, also analyzed by the MMRM method.

The trial data showed that at baseline, the mean PANSS total scores were 102.4 and 103.4 for the aripiprazole IM depot group and the placebo group, respectively. The mean baseline CGI-S score for both groups was 5.2, which indicates that subjects were markedly ill. For the primary efficacy endpoint assessed at Week 10, the treatment difference between the aripiprazole IM depot 400 mg/300 mg group and placebo was −15.1 and for the key secondary endpoint, the treatment difference between the aripirpazole IM depot 400

mg/300 mg group and the placebo was -0.8. Both results are statistically significant with p-value less than 0.0001 using the MMRM method.

Without any serious safety concern and based on significant efficacy findings, the sponsor concluded that aripiprazole IM depot provides an effective option for treatment of (b) (4) schizophrenia in adult patients, consistent with the well-established efficacy and safety profile of the oral formulation.

2.2 DATA SOURCES

This NDA submission including trial data, clinical study reports and protocols is stored in the following link: \\CDSESUB1\evsprod\NDA202971\0055.

For Study 31-12-291, we noted that many more patients in aripiprazole group discontinued the study due to withdrawal consent than those in placebo. Thus, to help us understand the causes and the impact on the efficacy analysis, an information request (IR) was sent to the sponsor during the review cycle. The sponsor's response and data adding a variable for identifying patients who had not previously taken aripiprazole are stored in the following link: \\CDSESUB1\evsprod\NDA202971\0088.

3. STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

After evaluation, the submitted data and quality of analysis are deemed to be satisfactory.

3.2 EVALUATION OF EFFICACY

3.2.1 Description of Study 31-12-291

Study 31-12-291 was titled "A 12-week, Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Aripiprazole Intramuscular Depot (OPC-14597, Lu AF41155) in the Acute Treatment of Adults with Schizophrenia". It was conducted from October 12, 2012 to August 30, 2013, where fifty-five trial sites worldwide were approved to receive IMP for this trial and of these, 51 trial sites were open for enrollment, 44 trial sites screened subjects and 41 (37 in the US, 2 in Croatia and 2 in Latvia) trial sites enrolled subjects.

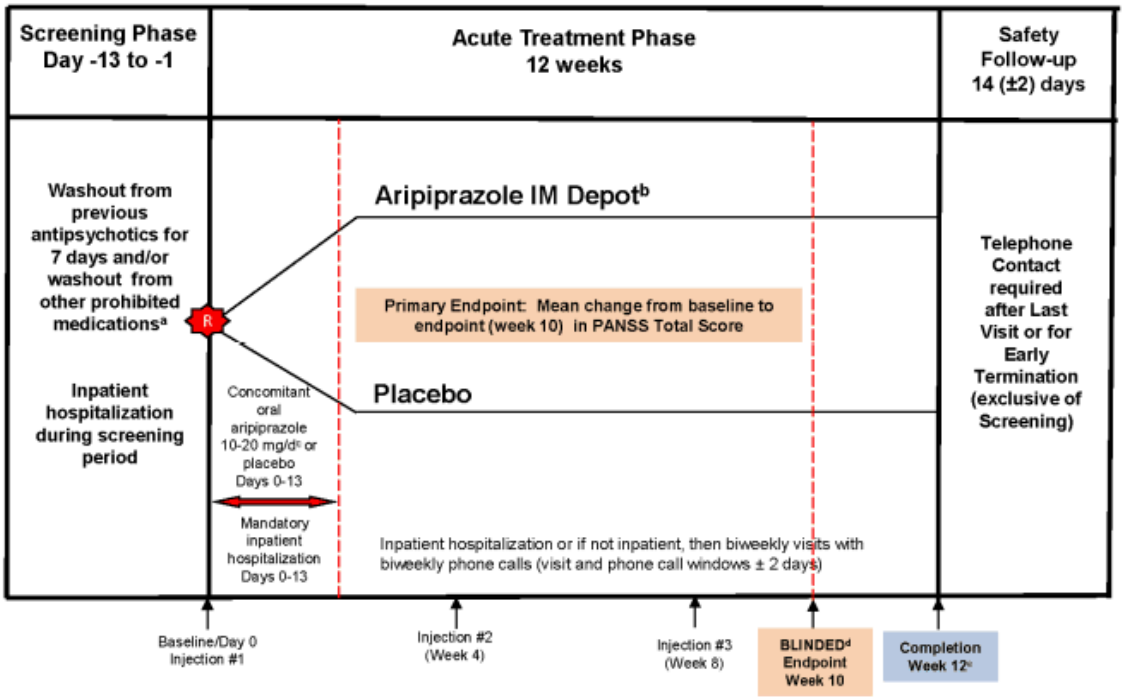
3.2.1.1 Study Objectives and Overall Design

The primary objective of this trial was to evaluate the overall efficacy of aripiprazole IM depot as acute treatment in subjects with schizophrenia.

The secondary objective of this trial was to evaluate the safety and tolerability of aripiprazole IM depot as acute treatment in subjects with schizophrenia.

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in adult male and female subjects between 18 and 65 years of age, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of schizophrenia for at least 1 year prior to screening who would benefit from hospitalization or continued hospitalization for the treatment of a current acute relapse of schizophrenia. The trial included a 13-day Screening Phase, a 12-week Acute Treatment Phase, and a 14 (±2)-day Safety Follow-up. No data monitoring committee was used in this trial. Figure 1 shows the schematic of the trial design (Screening Phase, Acute Treatment Phase and Safety Follow-up). Of note, during the first two weeks of acute treatment phase, patients could take concomitant oral aripiprazole 10-20 mg or Placebo.

Figure 1 Design Schematic for Study 31-12-291



Abbreviations: R = randomization; PANSS = Positive and Negative Syndrome Scale.
Note: The protocol defined Day 0 as the first day of dosing; however, for statistical analysis and data presented within this CSR, Day 0 was defined as the day prior to dosing with Day 1 being the first day of dosing.

[a] For subjects with no previous exposure to aripiprazole: 10 mg/day of oral aripiprazole for 3 days prior to 7 days of antipsychotic washout (prior to randomization) was administered. For subjects with previous exposure to aripiprazole: 7 days of antipsychotic washout (prior to randomization).

[b] 400 mg with allowed decrease to 300 mg for safety and return to 400 mg for efficacy if needed.

[c] Concomitant oral dosing was to be prescribed as outlined in the protocol (Section 16.1.1, Protocol Section 3.2.2.2).

[d] To minimize any potential bias, investigators and subjects were blinded to the primary efficacy endpoint (ie, change from baseline to Week 10).

[e] Completers of the Acute Treatment Phase (12 weeks) may have entered a 6-month open-label extension study (Trial 31-12-297) at the investigator's discretion.

Source: Figure 9.1-1 of CSR.

3.2.1.2 Efficacy Endpoints & Analyses

Although this trial was designed for up to 12 weeks of treatment for an acute episode of schizophrenia, the statistical inference primarily focused on the test of treatment effect at Week 10. The primary efficacy endpoint was the change from baseline to endpoint **(Week 10)** in PANSS total score. The key secondary efficacy endpoint was the change from baseline to endpoint **(Week 10)** in Clinical Global Impression – Severity (CGI-S).

Other secondary efficacy endpoints were as follows:

- Change from baseline to endpoint (Week 10) in PANSS positive and negative subscales
- Change from baseline to endpoint (Week 10) in Personal and Social Performance Scale (PSP)
- Clinical Global Impression - Improvement (CGI-I) score at endpoint (Week 10)
- Responder rate at endpoint (Week 10) (response defined by ≥30% reduction from baseline in PANSS total score)

The primary statistical comparison was performed using the Mixed Model Repeated Measure (MMRM) approach. Analyses included the categorically fixed effects of treatment, region (pooled sites), trial week, and treatment-by-week interaction, as well as the continuously fixed covariates of baseline score-by-week interaction. An unstructured covariance structure was used to model the within-subject errors and Kenward-Rodger degree of freedom was used to test the fixed effects.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

The patient disposition in the 12-week Acute Treatment Phase is summarized in Table 1. Three hundred forty subjects were randomized from 41 trial sites, where 168 subjects were randomly assigned to treatment with aripiprazole IM depot 400 mg/300 mg and 172 subjects to placebo during the 12-week Acute Treatment Phase. However, only 162 patients in aripiprazole IM depot 400 mg/300 mg and 167 patients in placebo group had post randomization measurement, so that only 329 patients belonged to the modified Intent to Treat (mITT) population, i.e., the primary efficacy sample.

The reasons for discontinuation by Week 10 are summarized in Table 2. Overall, 64.3% and 49.4% of subjects completed Week 10 in the aripiprazole IM depot 400 mg/300 mg and placebo groups, respectively. The most frequent cause of discontinuation by Week 10 in the placebo group was lack of efficacy (as determined by the investigator), which was 29.1% (50/172) but it was only 7.1% (12/168) in the aripiprazole IM depot 400 mg/300 mg group. In the aripiprazole IM depot 400 mg/300 mg group, the most common cause of discontinuation by Week 10 was the subject withdrew consent, where it was 19.0% versus 8.7% for placebo.

Table 1 Patient Disposition for Study 31-12-291

n (%)	Aripiprazole IM Depot 400/300 mg (N=168)	Placebo (N=172)	Total (N=340)
Screened			506
Screen Failure			166
Randomized	168 (100.0)	172 (100.0)	340 (100.0)
Modified Intent to Treat (ITT) Population	162 (96)	167 (97)	329 (97)
Completed	94 (56.0)	65 (37.8)	159 (46.8)
Discontinued	74 (44.0)	107 (62.2)	181 (53.2)
Analyzed for Safety	167 (99.4)	172 (100.0)	339 (99.7)
Analyzed for Efficacy	167 (99.4)	172 (100.0)	339 (99.7)

Source: Sponsor's Table 10.1-1 of clinical study report

Table 2 Reasons for Discontinuation by Week 10 for Study 31-12-291

n (%)	Aripiprazole IM Depot 400/300 mg (N=168)	Placebo (N=172)	Total (N=340)
Randomized	168 (100.0)	172 (100.0)	340 (100.0)
Completed Trial Week 10	108 (64.3)	85 (49.4)	193 (56.8)
Discontinued Prior to Trial Week 10	60 (35.7)	87 (50.6)	147 (43.2)
Lost to Follow-up	3 (1.8)	4 (2.3)	7 (2.1)
Adverse Events	7 (4.2)	13 (7.6)	20 (5.9)
Sponsor Discontinued Study	0 (0)	0 (0)	0 (0)
Subject Met Withdrawal Criteria	5 (3.0)	5 (2.9)	10 (2.9)
Investigator Withdrawal Subject	1 (0.6)	0 (0)	1 (0.3)
Subject Withdrawal Consent	32 (19)	15 (8.7)	47 (13.8)
Protocol Deviation	0 (0)	0 (0)	0 (0)
Lack of Efficacy as Determined by Investigator	12 (7.1)	50 (29.1)	62 (18.2)

Source: Sponsor's Table 10.1-2 of clinical study report

The demographic characteristics for randomized subjects were presented in Table 3. As seen from the table, patients' demographic characteristics were similar between two treatment groups. Most subjects randomized were male (79.1%), Black/African American (65.6%) and non-Hispanic/Latino (90.3%). The mean age was 42.4 years and mean BMI was 28.5 kg/m^2. Most subjects (96.2%) were enrolled in the US.

Table 3 Patients' Demographic Characteristics based on Randomized Sample for Study 31-12-291

Demographic Characteristics	Aripiprazole IM Depot 400/300 mg (N=168)	Placebo (N=172)	Total (N=340)
Age (years), mean (SD)	42.1 (11.0)	42.7 (10.9)	42.4 (11.0)
Age < 45 years, n (%)	88 (52.4)	89 (51.7)	177 (52.1)
Age ≥45 years, n (%)	80 (47.6)	83 (48.3)	163 (47.9)
Sex, n (%)			
Male	130 (77.4)	139 (80.8)	269 (79.1)
Female	38 (22.6)	33 (19.2)	71 (20.9)

Demographic Characteristics	Aripiprazole IM Depot 400/300 mg (N=168)	Placebo (N=172)	Total (N=340)
Race, n (%)			
White	52 (31.0)	55 (32.0)	107 (31.5)
Black or African American	110 (65.5)	113 (65.7)	223 (65.6)
Asian	2 (1.2)	0 (0.0)	2 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.6)	2 (1.2)	3 (0.9)
Other	3 (1.8)	2 (1.2)	5 (1.5)
Ethnicity, n (%)			
Hispanic or Latino	17 (10.1)	16 (9.3)	33 (9.7)
Not Hispanic or Latino	151 (89.9)	156 (90.7)	307 (90.3)
Region (Pooled Centers), n (%)			
US-Northeast	18 (10.7)	18 (10.5)	36 (10.6)
US-West	51 (30.4)	56 (32.6)	107 (31.5)
US-MID-West	15 (8.9)	15 (8.7)	30 (8.8)
US-South-Atlantic	42 (25.0)	42 (24.4)	84 (24.7)
US-South-Central	36 (21.4)	34 (19.8)	70 (20.6)
Europe	6 (3.6)	7 (4.1)	13 (3.8)
Country, n (%)			
Croatia	5 (3.0)	6 (3.5)	11 (3.2)
Latvia	1 (0.6)	1 (0.6)	2 (0.6)
United States	162 (96.4)	165 (95.9)	327 (96.2)
Weight (kg), mean (SD)	86.0 (17.7)	86.6 (16.7)	86.3 (17.2)
Height (cm), mean (SD)	174 (10.2)	174 (8.6)	174 (9.4)
Body Mass Index (kg/m^2), mean (SD)	28.4 (5.6)	28.5 (5.2)	28.5 (5.4)
BMI (kg/m^2) $\leq$ 28, n (%)	82 (48.8)	80 (46.5)	162 (47.6)
BMI (kg/m^2) > 28, n (%)	86 (51.2)	92 (53.5)	178 (52.4)

Note: Age, weight and BMI represent values at baseline
Source: Sponsor's Table 11.2-1 of clinical study report

3.2.3 Efficacy Results and Conclusions

3.2.3.1 Sponsor's Results for Primary Efficacy Endpoint

The sponsor's analysis results for the change from baseline to each study week in PANSS Total score by the MMRM method are presented in Table 4. For the primary endpoint, the treatment difference between the aripiprazole IM depot 400 mg/300 mg group (mean change -26.8) and the placebo group (mean change -11.7) at Week 10 was –15.1, which is statistically significant with $p<0.0001$. The treatment difference at Week 12 was -14.6, which was also statistically significant with $p<0.0001$.

The sponsor also performed sensitivity analyses by ANCOVA for the last observed carried forward data (ANCOVA-LOCF) and observed cases (ANCOVA-OC) data. Tables 5 and 6 display their results. As seen from the tables, both analysis results are very similar to those by MMRM; the p-values are less than 0.05 for all weeks.

Table 4 Sponsor's Results by MMRM for Change from Baseline in PANSS Total Score for Study 31-12-291

		Baseline Value		Change from Baseline		Comparisons	
Trial Week	Treatment Group	N	Mean (SD)	N	LS Mean (SE)	Difference	P-Value
Baseline	ARIP IMD	162	102.4 (11.4)				
	Placebo	167	103.4 (11.1)				
Week 1	ARIP IMD	162	93.8 (14.2)	162	-8.9 (0.9)	-3.9	0.0005
	Placebo	167	98.9 (15.9)	167	-5.0 (0.9)		
Week 2	ARIP IMD	144	87.2 (16.1)	144	-15.2 (1.2)	-7.0	<0.0001
	Placebo	157	94.8 (17.0)	157	-8.3 (1.2)		
Week 4	ARIP IMD	134	82.6 (16.8)	134	-19.0 (1.4)	-9.2	<0.0001
	Placebo	140	91.9 (18.1)	140	-9.8 (1.3)		
Week 6	ARIP IMD	126	78.3 (16.3)	126	-21.5 (1.5)	-11.1	<0.0001
	Placebo	117	89.8 (18.2)	117	-10.3 (1.5)		
Week 8	ARIP IMD	108	74.1 (15.3)	108	-23.7 (1.6)	-14.0	<0.0001
	Placebo	96	88.3 (19.9)	96	-9.7 (1.6)		
Week 10	ARIP IMD	99	70.6 (15.2)	99	-26.8 (1.6)	-15.1	<0.0001
	Placebo	81	85.6 (18.4)	81	-11.7 (1.6)		
Week 12	ARIP IMD	99	70.6 (16.4)	99	-27.2 (1.7)	-14.6	<0.0001
	Placebo	68	83.7 (18.4)	68	-12.6 (1.8)		

Source: Table 11.4.1.1-1 of CSR

Note: LS Mean, SE and p-value were derived from an MMRM analysis with fixed effects of treatment, region (pooled sites), week, treatment by week interaction and baseline by week interaction as covariate. Unstructured covariance structure for observations within a subject was used.

Table 5 Sponsor's Results by ANCOVA-LOCF for Change from Baseline in PANSS Total Score for Study 31-12-291

		Baseline Value		Change from Baseline		Comparisons	
Trial Week	Treatment Group	N	Mean (SD)	N	LS Mean (SE)	Difference	P-Value
Baseline	ARIP IMD	162	102.4 (11.4)				
	Placebo	167	103.4 (11.1)				
Week 1	ARIP IMD	162	93.8 (14.2)	162	-8.7 (0.9)	-3.9	0.0005
	Placebo	167	98.9 (15.9)	167	-4.8 (0.9)		
Week 2	ARIP IMD	162	88.0 (16.1)	162	-15.4 (1.2)	-6.6	<0.0001
	Placebo	167	95.6 (17.6)	167	-8.8 (1.2)		
Week 4	ARIP IMD	162	84.9 (17.6)	162	-18.6 (1.4)	-8.6	<0.0001
	Placebo	167	94.5 (19.5)	167	-10.1 (1.4)		
Week 6	ARIP IMD	162	83.2 (18.7)	162	-20.9 (1.5)	-10.0	<0.0001
	Placebo	167	94.2 (20.3)	167	-10.9 (1.5)		
Week 8	ARIP IMD	162	81.8 (19.2)	162	-22.8 (1.6)	-12.0	<0.0001
	Placebo	167	94.7 (21.6)	167	-10.9 (1.6)		
Week 10	ARIP IMD	162	80.4 (20.0)	162	-24.4 (1.6)	-12.8	<0.0001
	Placebo	167	94.2 (21.0)	167	-11.6 (1.6)		
Week 12	ARIP IMD	162	80.1 (20.6)	162	-24.8 (1.7)	-12.7	<0.0001
	Placebo	167	93.8 (21.6)	167	-12.1 (1.6)		

Source: Table CT-5.1.2 of CSR

Table 6 Sponsor's Results by ANCOVA-OC for Change from Baseline in PANSS Total Score for Study 31-12-291

		Baseline Value		Change from Baseline		Comparisons	
Trial Week	Treatment Group	N	Mean (SD)	N	LS Mean (SE)	Difference	P-Value
Baseline	ARIP IMD	162	102.4 (11.4)				
	Placebo	167	103.4 (11.1)				
Week 1	ARIP IMD	162	93.8 (14.2)	162	-8.7 (0.9)	-3.9	0.0005
	Placebo	167	98.9 (15.9)	167	-4.8 (0.9)		
Week 2	ARIP IMD	144	87.2 (16.1)	144	-16.9 (1.2)	-7.1	<0.0001
	Placebo	157	94.8 (17.0)	157	-9.7 (1.2)		
Week 4	ARIP IMD	134	82.6 (16.8)	134	-20.9 (1.4)	-9.4	<0.0001
	Placebo	140	91.9 (18.1)	140	-11.5 (1.4)		
Week 6	ARIP IMD	126	78.3 (16.3)	126	-25.2 (1.5)	-11.7	<0.0001
	Placebo	117	89.8 (18.2)	117	-13.5 (1.6)		
Week 8	ARIP IMD	108	74.1 (15.3)	108	-29.3 (1.8)	-14.2	<0.0001
	Placebo	96	88.3 (19.9)	96	-15.1 (1.9)		
Week 10	ARIP IMD	99	70.6 (15.2)	99	-32.1 (1.7)	-14.4	<0.0001
	Placebo	81	85.6 (18.4)	81	-17.7 (2.0)		
Week 12	ARIP IMD	99	70.6 (16.4)	99	-32.8 (1.8)	-13.0	<0.0001
	Placebo	68	83.7 (18.4)	68	-19.8 (2.1)		

Source: Table CT-5.1.3 of CSR

3.2.3.2 Sponsor's Results for Secondary Efficacy Endpoints

Tables 7 to 9 present the sponsor's results for the secondary endpoint: change from baseline in CGI-severity score (Note: this is Key secondary endpoint), change from baseline to endpoint in PANSS Positive Subscale Score, change from baseline to endpoint in PANSS Negative Subscale Score for each study week.

Table 7 Sponsor's Results by MMRM for Change from Baseline in CGI-Severity Score for Study 31-12-291

		Baseline Value		Change from Baseline		Comparisons	
Trial Week	Treatment Group	N	Mean (SD)	N	LS Mean (SE)	Difference	P-Value
Baseline	ARIP IMD	162	5.2 (0.5)				
	Placebo	168	5.2 (0.5)				
Week 1	ARIP IMD	162	4.8 (0.7)	162	-0.4 (0.1)	-0.3	0.0001
	Placebo	168	5.1 (0.6)	168	-0.2 (0.1)		
Week 2	ARIP IMD	144	4.4 (0.9)	144	-0.8 (0.1)	-0.4	<0.0001
	Placebo	157	4.9 (0.7)	157	-0.4 (0.1)		
Week 4	ARIP IMD	134	4.2 (0.9)	134	-1.0 (0.1)	-0.6	<0.0001
	Placebo	140	4.8 (0.8)	140	-0.4 (0.1)		
Week 6	ARIP IMD	126	4.0 (0.9)	126	-1.2 (0.1)	-0.7	<0.0001
	Placebo	117	4.6 (0.9)	117	-0.5 (0.1)		
Week 8	ARIP IMD	108	3.8 (0.9)	108	-1.3 (0.1)	-0.7	<0.0001
	Placebo	96	4.5 (1.0)	96	-0.6 (0.1)		
Week 10	ARIP IMD	99	3.6 (0.8)	99	-1.4 (0.1)	-0.8	<0.0001
	Placebo	81	4.4 (1.0)	81	-0.6 (0.1)		
Week 12	ARIP IMD	99	3.6 (0.9)	99	-1.4 (0.1)	-0.8	<0.0001
	Placebo	68	4.3 (1.0)	68	-0.6 (0.1)		

Source: Table 11.4.1.2.1-1 of CSR

Table 8 Sponsor's Results by MMRM for Change from Baseline in PANSS Positive Subscale Score for Study 31-12-291

		Baseline Value		Change from Baseline		Comparisons	
Trial Week	Treatment Group	N	Mean (SD)	N	LS Mean (SE)	Difference	P-Value
Baseline	ARIP IMD	162	29.5 (3.3)				
	Placebo	167	29.4 (3.0)				
Week 1	ARIP IMD	162	26.2 (4.8)	162	-3.3 (3.7)	-1.4	0.0006
	Placebo	167	27.5 (4.7)	167	-1.9 (3.5)		
Week 2	ARIP IMD	144	23.8 (5.1)	144	-5.6 (4.6)	-2.3	<0.0001
	Placebo	157	26.0 (5.1)	157	-3.3 (4.5)		
Week 4	ARIP IMD	134	22.4 (5.9)	134	-7.0 (5.0)	-3.1	<0.0001
	Placebo	140	25.1 (5.7)	140	-4.0 (5.2)		
Week 6	ARIP IMD	126	20.8 (6.0)	126	-8.5 (5.0)	-3.8	<0.0001
	Placebo	117	24.3 (5.6)	117	-4.8 (5.4)		
Week 8	ARIP IMD	108	19.3 (5.4)	108	-9.9 (4.8)	-4.8	<0.0001
	Placebo	96	24.1 (6.6)	96	-5.0 (6.3)		
Week 10	ARIP IMD	99	18.2 (5.3)	99	-10.8 (4.7)	-5.1	<0.0001
	Placebo	81	23.0 (6.2)	81	-6.2 (5.8)		
Week 12	ARIP IMD	99	18.4 (5.6)	99	-10.7 (5.0)	-5.1	<0.0001
	Placebo	68	22.6 (6.4)	68	-6.9 (5.9)		

Source: Table 11.4.1.2.2.1-1 of CSR

Table 9 Sponsor's Results by MMRM for Change from Baseline in PANSS Negative Subscale Score for Study 31-12-291

		Baseline Value		Change from Baseline		Comparisons	
Trial Week	Treatment Group	N	Mean (SD)	N	LS Mean (SE)	Difference	P-Value
Baseline	ARIP IMD	162	23.7 (4.7)				
	Placebo	167	24.6 (4.5)				
Week 1	ARIP IMD	162	22.2 (4.6)	162	-1.6 (0.2)	-0.9	0.0023
	Placebo	167	24.0 (5.3)	167	-0.7 (0.2)		
Week 2	ARIP IMD	144	21.3 (4.9)	144	-2.4 (0.3)	-1.2	0.0032
	Placebo	157	23.3 (5.5)	157	-1.2 (0.3)		
Week 4	ARIP IMD	134	20.4 (4.6)	134	-3.1 (0.4)	-1.8	0.0003
	Placebo	140	22.8 (5.6)	140	-1.3 (0.4)		
Week 6	ARIP IMD	126	19.7 (4.6)	126	-3.5 (0.4)	-2.2	<0.0001
	Placebo	117	22.6 (5.1)	117	-1.3 (0.4)		
Week 8	ARIP IMD	108	18.8 (4.4)	108	-4.0 (0.4)	-2.6	<0.0001
	Placebo	96	22.0 (5.4)	96	-1.4 (0.4)		
Week 10	ARIP IMD	99	18.2 (4.5)	99	-4.5 (0.5)	-2.8	<0.0001
	Placebo	81	21.5 (5.7)	81	-1.6 (0.5)		
Week 12	ARIP IMD	99	18.0 (4.5)	99	-4.7 (0.4)	-2.5	<0.0001
	Placebo	68	20.6 (5.0)	68	-2.2 (0.5)		

Source: Table 11.4.1.2.2.2-1 of CSR

Tables 10 to 12 present the sponsor's results for change from baseline to Weeks 10 and 12, separately in PSP score, the summaries of CGI Improvement Score and the responder rate based on PANSS Total Score. As seen from the tables, the differences between the aripiprazole IM depot and placebo are all statistically significant, with p-value <0.0001.

Table 10 Sponsor's LOCF Results for Change from Baseline to Weeks 10 and 12 in PSP Score for Study 31-12-291

		Baseline Value		Change from Baseline		Comparisons
Trial Week	**Treatment Group**	**N**	**Mean (SD)**	**N**	**LS Mean (SE)**	**Difference (95% C.I.)**
Week 10	ARIP IMD	99	43.7 (9.4)	99	12.3	7.1
	Placebo	81	42.6 (9.7)	81	5.2	(4.1, 10.1)
Week 12	ARIP IMD	99	43.7 (9.4)	99	13.0	7.5
	Placebo	68	42.6 (9.7)	68	5.5	(4.6, 10.5)

Source: Table CT-5.9.1 & 5.9.2 of CSR

Table 11 Sponsor's Summary of CGI Improvement Score by LOCF for Study 31-12-291

Trial Week	**Treatment Group**	**N**	**Mean (SD)**	**P-Value**
Week 1	ARIP IMD	158	3.4 (0.8)	<0.0001
	Placebo	164	3.9 (0.8)	
Week 2	ARIP IMD	162	3.0 (0.9)	<0.0001
	Placebo	168	3.8 (1.0)	
Week 4	ARIP IMD	162	2.9 (1.0)	<0.0001
	Placebo	168	3.7 (1.1)	
Week 6	ARIP IMD	162	2.8 (1.1)	<0.0001
	Placebo	168	3.7 (1.2)	
Week 8	ARIP IMD	162	2.7 (1.2)	<0.0001
	Placebo	168	3.8 (1.3)	
Week 10	ARIP IMD	162	2.7 (1.2)	<0.0001
	Placebo	168	3.7 (1.3)	
Week 12	ARIP IMD	162	2.6 (1.2)	<0.0001
	Placebo	168	3.7 (1.3)	

Source: Table 11.4.1.2.2.4-1 of CSR

Table 12 Sponsor's Summary of Responder Rate Based on PANSS Total Score-LOCF (Efficacy Sample) for Study 31-12-291

		Value		Comparisons (vs Placebo)		
Trial Week	**Treatment Group**	**N**	**N (%)**	**Difference (%) (95% C.I.)**	**P-Value (CMH)**	**P-Value (Fisher)**
Week 1	ARIP IMD	162	8 (4.9)	3.1	0.1250	0.1341
	Placebo	167	3 (1.8)	(-1.4, 7.6)		
Week 2	ARIP IMD	162	21 (13.0)	4.6	0.2059	0.2117
	Placebo	167	14 (8.4)	(-2.7, 11.9)		
Week 4	ARIP IMD	162	28 (17.3)	7.1	0.0695	0.0771
	Placebo	167	17 (10.2)	(-0.9, 15.1)		
Week 6	ARIP IMD	162	36 (22.2)	8.4	0.0530	0.0611
	Placebo	167	23 (13.8)	(-0.4, 17.3)		
Week 8	ARIP IMD	162	46 (28.4)	14.6	0.0013	0.0012
	Placebo	167	23 (13.8)	(5.3, 23.9)		
Week 10	ARIP IMD	162	60 (37.0)	22.7	<0.0001	<0.0001
	Placebo	167	24 (14.4)	(12.9, 32.4)		
Week 12	ARIP IMD	162	56 (34.6)	19.0	<0.0001	<0.0001
	Placebo	167	26 (15.6)	(9.2, 28.8)		

Source: Table 11.4.1.2.2.5-1 of CSR

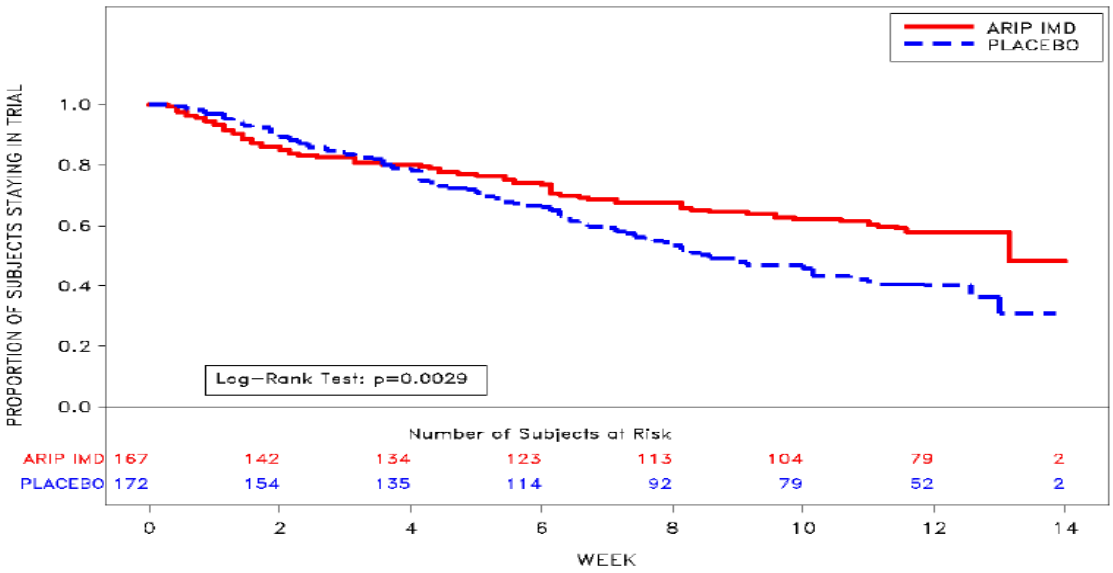
3.2.3.3 Sponsor's Conclusions

The sponsor concluded that aripiprazole IM depot 400 mg/300 mg administered as a monthly injection was efficacious for the treatment of [redacted] (b) (4) schizophrenia in adult subjects as demonstrated by superiority to placebo in the primary efficacy endpoint, change from baseline to endpoint (Week 10) in PANSS total score as well as the key secondary endpoint: change from baseline to endpoint (Week 10) in CGI-S score and other secondary endpoints including mean change from baseline to endpoint (Week 10) in PANSS positive and negative subscales and the PSP scores, mean CGI-I score at endpoint (Week 10), and responder rate at endpoint (Week 10) (response defined by ≥30 % reduction in PANSS total score, CGI-I score of 1 or 2, and ≥30% reduction in PANSS total score or CGI-I score of 1 or 2).

3.2.3.4 Statistical Reviewer's Findings and Comments

1. The statistical reviewer confirmed most of the sponsor's analysis results and agreed that the data of Study 31-12-291 support the aripiprazole IM depot 400 mg/300 mg's efficacy in treating patients with schizophrenia based on the prospectively specified efficacy endpoints. Nevertheless, one should note that although the overall discontinuation rate in the aripiprazole IM depot 400 mg/300 mg group is lower than placebo (35.7% vs. 50.6%), which is not unusual for schizophrenia trials, those in the aripiprazole IM depot 400 mg/300 mg group who dropped out due to withdrawal consent is much higher (19% vs. 8.7%) than placebo. In addition, most dropouts in the aripiprazole IM depot 400 mg/300 mg group occurred earlier than placebo before Week 4, which can be observed from the sponsor's time to discontinuation plot in Figure 2 below.

Figure 2 Sponsor's Kaplan-Meier Product Limit Plot of Time to Discontinuation Due to All Reasons



Source: Sponsor's Figure 11.4.1.3.1-1

2. Regarding the efficacy of aripiprazole IM depot 400 mg/300 mg, the statistical reviewer found that the following statement in the labeling (b) (4)

[redacted]

3. As mentioned earlier in Section 3.2.2, based on Table 2, even though placebo patients had larger dropout rate than aripiprazole patients (62% versus 44%), like many schizophrenia trials, there were many more dropouts due to withdrawal consent at Week 10 in aripiprazole group than those in placebo group (19% versus 8.7%). To better understand the causes and the impact on the efficacy analysis results, we asked the sponsor to perform some exploratory analyses. Our request and the sponsor's response are shown in the following:

- **FDA Question about subjects dropping out due to withdrawal consent :** We are concerned about the number of discontinuations due to "subject withdrew consent" in Study 31-12-291 and the fact that they occurred in the drug group at twice the rate of the placebo group (19% for Arip. IMD; 8.7% for placebo). To help us understand the possible causes, please submit the following information:

  a. For all discontinuations due to "subject withdrew consent", please indicate the number and percent of subjects (by treatment group) who were aripiprazole naïve (meaning those who had not previously been treated with aripiprazole prior to entry into Study 31-12-291). In addition, please indicate the total number and percent of subjects (by treatment group) in the intent-to-treat population who were aripiprazole naïve.

  b. Please indicate the ID number of all subjects in the intent-to-treat population who were aripiprazole naïve, and submit a revised panss0.xpt data set by adding a variable to indicate aripiprazole naïve patients.

  c. Refer to Table 10.1-2 entitled "*Reasons for Discontinuation by Week 10 – Primary Efficacy Endpoint (Randomized Sample)*" of your study report. Please provide a similar table but for the subgroups of aripiprazole naïve and non-naïve patients.

  d. Refer to the pre-specified primary analysis of the primary endpoint. Please perform exploratory subgroup analysis by whether patients were aripirpazole naïve or not.

- **Sponsor's Response**

a. Per the statistical analysis plan, the randomized sample is the same as the intent-to-treat population.

*Table 1.1 entitled "Reasons for Discontinuation by Treatment Group and Previous Exposure to Aripiprazole (Randomized Sample)" provides the subjects who withdrew consent by aripiprazole naïve versus non-naïve subjects by treatment group overall (up to **Week 12**). Of subjects who withdrew consent overall (up to Week 12), aripiprazole IM depot group has 22/99 (22.2%) aripiprazole naïve subjects (not exposed) and 13/69 (18.8%) non-naïve subjects (exposed); the placebo group has 7/96 (7.3%) aripiprazole naïve subjects (not exposed) and 10/76 (13.2%) non-naïve subjects (exposed).*

Aripiprazole naïve subjects enrolled in the trial are noted in Table 1.2 (99/168, 58.9% of aripiprazole IM depot subjects and 96/172, 55.8% of placebo subjects).

b. Table 3 entitled "Trial Completion Status and Reasons for Discontinuation by Treatment Group and Previous Exposure to Aripiprazole (Randomized Sample)" provides the information requested. Revised data set is provided in Section 5.3.5.1 (see panss0.xpt; variable exparip added).

*c. Table 2 entitled "Reasons for Discontinuation by Trial Week 10 by Treatment Group and Previous Exposure to Aripiprazole (Randomized Sample)" provides the subjects who withdrew consent by aripiprazole naïve versus non-naïve subjects by treatment group up to **Week 10**. Of subjects who withdrew consent (up to Week 10), aripiprazole IM depot group has 19/99 (19.2%) aripiprazole naïve subjects (not exposed) and 13/69 (18.8%) non-naïve subjects (exposed); the placebo group has 6/96 (6.3%) aripiprazole naïve subjects (not exposed) and 9/76 (11.8%) non-naïve subjects(exposed).*

d. Per request, please see new tables for the primary endpoint (MMRM, LOCF and OC) by aripiprazole naïve subjects versus non-naïve subjects.

Table 4.1 entitled "Summary of Change from Baseline in PANSS Total Score by Previous Exposure to Aripiprazole – MMRM (Efficacy Sample)" contains the MMRM analysis. For the MMRM analysis, aripiprazole naïve subjects (not exposed) had a difference in PANSS Total Score of -17.5 at Week 10 between the aripiprazole IM depot versus placebo group (p-value <0.0001); non-naive subjects (exposed) had a difference in PANSS Total Score of -12.2 between the treatment groups (p-value 0.0010).

Table 4.2 entitled "Summary of Change from Baseline in PANSS Total Score by Previous Exposure to Aripiprazole – LOCF (Efficacy Sample)" contains the LOCF analysis. Aripiprazole naïve subjects (not exposed) had a difference in PANSS Total Score of -16.0 at Week 10 between the aripiprazole IM depot versus placebo group (p-value <0.0001); non-naive subjects (exposed) had a difference in PANSS Total Score of -8.9 between the treatment groups (p-value 0.0034).

(Note that: The aforementioned Tables 1.1, 1.2, 2 and 4.1 are shown as Tables 14, 15, 16 and 13 in the Appendix of Section 6 and Section 4.2.2. The aforementioned Tables 3 and 4.2 were not shown in this review.)

According to Table 14, we noted that among 35 aripiprazole dropouts due to withdrawal consent, 22 (63%) of them did not have any previous aripiprazole exposure but 13 (37%) of them did and among 17 placebo dropouts due to withdrawal consent, only 7 (41%) of them did not have any previous aripiprazole exposure but 10 (58.8%) did. In other words, although based on Table 15, it does not appear to have any difference between treatment groups in terms of proportion of patients who had or did not have aripiprazole exposure, more aripiprazole naïve patients dropped out due to withdrawal consent than those who were not aripiprazole naïve patients when given aripiprazole IMD. Actually, if we do not consider reasons, more aripiprazole naïve patients dropped out than those who were not aripiprazole naïve patients. Nevertheless, this phenomenon did not occur among those placebo dropouts due to withdrawal consent although among placebo dropouts, there were still about 60% of them who belong to aripiprazole naïve patients and 40% of them had previous aripiprazole exposure, which is similar to what was observed from the aripiprazole dropouts.

With regard to the impact of 60% aripiprazole naïve patients in the study, we noted that the aripiprazole IMD had larger effect in these patients than those who had previous exposure of aripiprazole although the aripiprazole IMD appeared to be effective in both subgroups. The detailed analysis results by MMRM from the sponsor are shown in Section 4.2.2.

3.3 EVALUATION OF SAFETY

This review does not contain any safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

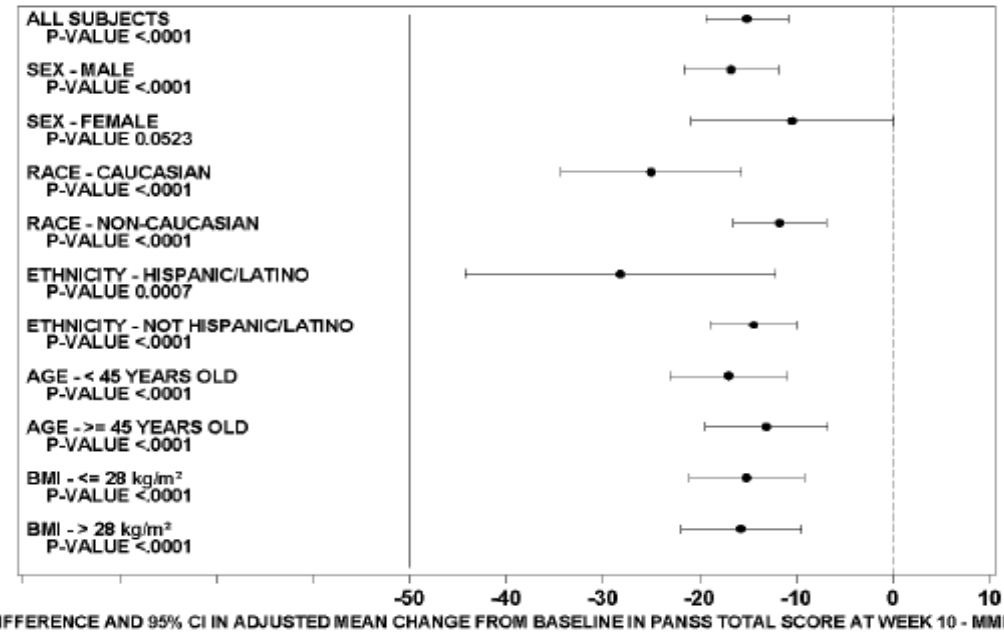
The sponsor performed the subgroup analyses for gender (male, female), race (Caucasian, non-Caucasian), age (<45 years, ≥45 years), ethnicity (Hispanic/Latino, Not Hispanic/ Latino), and BMI (≤28 kg/m^2, >28 kg/m^2) at baseline for the change from baseline to endpoint (Week 10) in PANSS total score (primary efficacy endpoint), for the change from baseline to endpoint in CGI-S (key secondary efficacy endpoint), and responder rate based on the different responder definitions by trial week. The statistical reviewer confirmed the sponsor's results, but only those for the primary endpoint and the key secondary endpoint are presented in this review. As none of the following subgroup analyses were prospectively planned to be examined in terms of study-wise type I error rate control, they were all performed for the purpose of exploration.

4.1 GENDER, RACE AND AGE

Based on Figures 3 and 4, the sponsor's subgroup analysis results for gender, race, ethnicity, age and BMI, they concluded that for all of the aforementioned subgroup categories examined on the change from baseline in PANSS total score and also CGI-S at

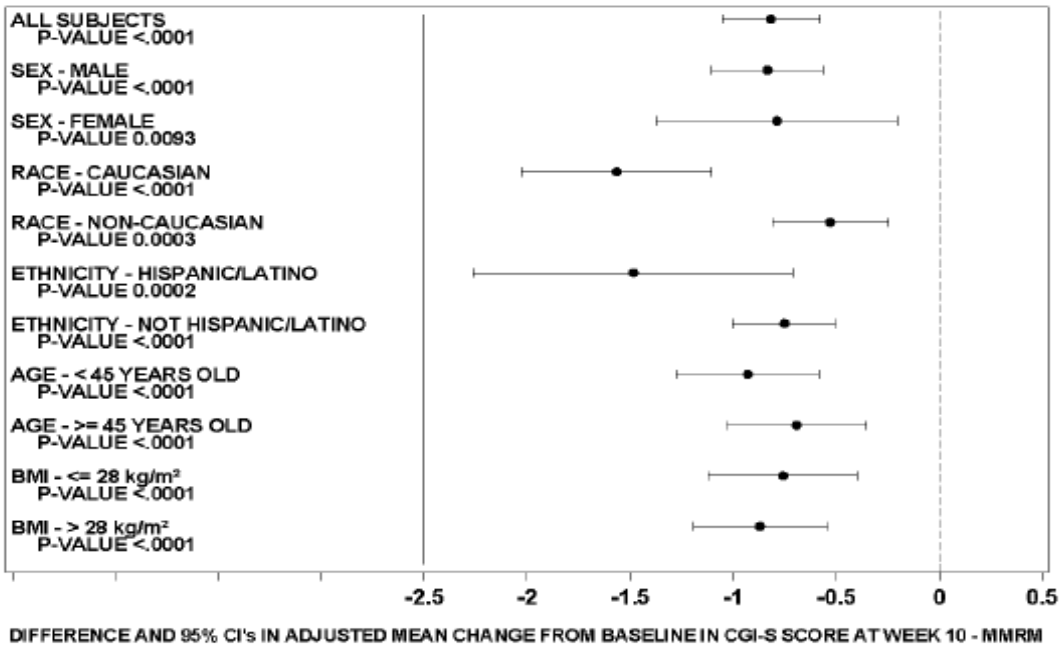
Week 10, the aripiprazole IM depot 400 mg/300 mg showed better performance than placebo.

Figure 3 Sponsor's Subgroup Analysis Results on PANSS Total at Week 10 for Study 31-12-291



Source: Figure 11.4.1.3.2.1-1 of clinical study report

Figure 4 Sponsor's Subgroup Analysis Results on CGI-S score at Week 10 for Study 31-12-291



Source: Figure 11.4.1.3.2.2-1 of clinical study report

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

4.2.2 Previous Exposure to Aripiprazole

The following Table 13 shows the sponsor's exploratory analyses for patients who had or did not have previous aripiprazole exposure. These analyses were performed to understand why there were more aripiprazole dropouts due to patient withdrawal consent than placebo dropouts. See the detailed explanation on the statistical reviewer's Comment #3 of Section 3.2.3.4.

Table 13 Sponsor's Subgroup Analysis Results for Patients' Previous Aripiprazole Exposure by MMRM for Study 31-12-291

With Previous Exposure to Aripiprazole		Change from Baseline		Comparisons	
Week	Treatment Group	N	LS Mean (SE)	Difference	95% C.I.
Week 1	ARIP IMD	66	-7.9 (1.2)	-2.8	(-6.2, 0.6)
	Placebo	73	-5.1 (1.2)		
Week 2	ARIP IMD	58	-14.2 (1.7)	-3.8	(-8.5, 0.8)
	Placebo	70	-10.4 (1.6)		
Week 3	ARIP IMD	53	-16.7 (2.0)	-4.7	(-10.2, 0.7)
	Placebo	61	-12.0 (1.9)		
Week 6	ARIP IMD	50	-19.1 (2.2)	-6.5	(-12.3, -0.6)
	Placebo	51	-12.6 (2.0)		
Week 8	ARIP IMD	42	-21.4 (2.6)	-10.6	(-17.8, -3.3)
	Placebo	43	-10.8 (2.5)		
Week 10	ARIP IMD	39	-24.1 (2.6)	-12.2	(-19.4, -5.1)
	Placebo	39	-11.8 (2.5)		
Week 12	ARIP IMD	38	-25.4 (2.7)	-12.4	(-20.1, -4.8)
	Placebo	33	-13.0 (2.7)		
Without Previous Exposure to Aripiprazole		Change from Baseline		Comparisons	
Week	Treatment Group	N	LS Mean (SE)	Difference	SE
Week 1	ARIP IMD	96	-9.1 (1.1)	-5.1	(-8.1, -2.1)
	Placebo	94	-4.0 (1.1)		
Week 2	ARIP IMD	86	-15.4 (1.5)	-9.9	(-14.0, -5.8)
	Placebo	87	-5.5 (1.5)		
Week 4	ARIP IMD	81	-19.9 (1.8)	-12.9	(-17.8, -7.9)
	Placebo	79	-7.1 (1.8)		
Week 6	ARIP IMD	76	-22.4 (1.9)	-14.8	(-20.1, -9.5)
	Placebo	66	-7.6 (1.9)		
Week 8	ARIP IMD	66	-24.5 (2.1)	-16.8	(-22.6, -10.9)
	Placebo	53	-7.7 (2.1)		
Week 10	ARIP IMD	60	-27.7 (2.0)	-17.5	(-23.4, -11.7)
	Placebo	42	-10.2 (2.2)		
Week 12	ARIP IMD	61	-27.3 (2.2)	-17.0	(-23.4, -10.7)
	Placebo	35	-10.3 (2.4)		

Source: Sponsor's Table 4.1 of IR response from 008 submission.

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The statistical reviewer has confirmed the sponsor's efficacy results on most important endpoints for Study 31-12-291 and agreed that the data support the efficacy of ABILIFY® MAINTENA™ (aripiprazole) in treating patients with schizophrenia based on the primary and key secondary endpoints. (b) (4)

5.2 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted a single phase 3 trial to demonstrate the efficacy of ABILIFY® MAINTENA™ (aripiprazole) as (b) (4) treatment of schizophrenia. After evaluation, the statistical reviewer agreed with the sponsor's efficacy findings at Week 10 based on the PANSS total score and the CGI-S score, (b) (4)

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Mathematical Statistician

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HFD-710/Dr. Hung
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Appendix

Table 14 Reasons for Discontinuation by Treatment Group and Previous Exposure to Aripiprazole (Randomized Sample)

n (%)	ARIP IMD			Placebo		
	Exposed (N=69)	Not Exposed (N=99)	Total (N=168)	Exposed (N=76)	Not Exposed (N=96)	Total (N=172)
Randomized	69 (100)	99 (100)	168 (100)	76 (100)	96 (100)	172 (100)
Completed	37 (53.6)	57 (57.6)	94 (56.0)	32 (42.1)	33 (34.4)	65 (37.8)
Discontinued	32 (46.4)	42 (42.4)	74 (44.0)	44 (57.9)	63 (65.6)	107 (62.2)
Lost to Follow Up	3 (4.3)	6 (6.1)	9 (5.4)	4 (5.3)	6 (6.3)	10 (5.8)
Adverse Events	4 (5.8)	3 (3.0)	7 (4.2)	6 (7.9)	7 (7.3)	13 (7.6)
Sponsor Discontinued Study	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subject Met Withdrawal Criteria	6 (8.7)	1 (1)	7 (4.2)	2 (2.6)	4 (4.2)	6 (3.5)
Investigator Withdrew Subject	1 (1.4)	0 (0)	1 (0.6)	1 (1.3)	0 (0)	1 (0.6)
Subject Withdrew Consent	13 (18.8)	22 (22.2)	35 (20.8)	10 (13.2)	7 (7.3)	17 (9.9)
Protocol Deviation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lack of Efficacy as Determined by the Investigator	5 (7.2)	10 (10.1)	15 (8.9)	21 (27.6)	39 (40.6)	60 (34.9)

Source: Sponsor's Table 1.1 of IR response from 008 submission.

Table 15 Summary of Previous Exposure to Aripiprazole

Previous Exposure To Aripiprazole	ARIP IMD (N=168)	Placebo (N=172)	Total (N=340)
Yes	69 (41.1)	76 (44.2)	145 (42.6)
No	99 (58.9)	96 (55.8)	195 (57.4)
Total	168 (100)	172 (100)	340 (100)

Source: Sponsor's Table 1.2 of IR response from 008 submission.

Table 16 Reasons for Discontinuation by Week 10 and by Treatment Group and Previous Exposure to Aripiprazole (Randomized Sample)

n (%)	ARIP IMD			Placebo		
	Exposed (N=69)	Not Exposed (N=99)	Total (N=168)	Exposed (N=76)	Not Exposed (N=96)	Total (N=172)
Randomized	69 (100)	99 (100)	168 (100)	76 (100)	96 (100)	172 (100)
Completed	40 (58)	68 (68.7)	108 (64.3)	41 (53.9)	44 (45.8)	85 (49.4)
Discontinued	29 (42)	31 (31.3)	60 (35.7)	35 (46.1)	52 (54.2)	87 (50.6)
Lost to Follow Up	2 (2.9)	1 (1.0)	3 (1.8)	2 (2.6)	2 (2.1)	4 (2.3)
Adverse Events	4 (5.8)	3 (3.0)	7 (4.2)	6 (7.9)	7 (7.3)	13 (7.6)
Sponsor Discontinued Study	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subject Met Withdrawal Criteria	5 (7.2)	0 (0)	5 (3.0)	2 (2.6)	3 (3.1)	5 (2.9)
Investigator Withdrew Subject	1 (1.4)	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)
Subject Withdrew Consent	13 (18.8)	19 (19.2)	32 (19.0)	9 (11.8)	6 (6.3)	15 (8.7)
Protocol Deviation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lack of Efficacy as Determined by the Investigator	4 (5.8)	8 (8.1)	12 (7.1)	16 (21.1)	34 (35.4)	50 (29.1)

Source: Sponsor's Table 2 of IR response from 008 submission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YEH FONG CHEN
09/02/2014

PEILING YANG
09/02/2014

KOOROS MAHJOOB
09/02/2014
I concuuur with the review.