CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S-018

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/Serial Number:	21-436 / S_018
Drug Name:	Abilify (aripiprazole)
Indication(s):	Aripiprazole as Adjunctive Treatment of Major Depressive Disorder
Applicant:	Bristol-Myers Squibb
Date(s):	Date of Document: 5/16/2007 PDUFA due date: 11/16/2007
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Keywords:	Multiple comparison, interaction

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The two identical placebo-controlled clinical trials support the efficacy claim of aripiprazole as an adjunct to antidepressants in treating patients with Major Depression Disorder (MDD).

The primary endpoint, mean change from end of 8-week Prospective Treatment Phase (Phase B) to Week 14 (LOCF) in the MADRS Total Score, is statistically significant in both trials. The key secondary endpoint is on the borderline in Study 138139 but statistically significant in Study 138163. The reviewer found a potential interaction between treatment and gender in Study 138139. However, the treatment-by-gender interaction does not show in Study 138163. Given that two studies are not consistent on this matter and the sample size of males is relatively smaller than females in Study 138139, it remains inconclusive whether there exists the treatment-by-gender interaction at this stage.

1.2 Brief Overview of Clinical Studies

This sNDA includes two identical placebo-controlled studies (CN 138139 and CN 138163) for approval of Abilify (aripiprazole) as an adjunct to antidepressants in the treatment of patients with MDD.

Eligible patients were enrolled into the Phase B and were dispensed single-blind placebo plus an assigned open-label marketed antidepressant therapy (ADT). Patients who completed Phase B and met criteria for an incomplete response were randomized into the 6-week double-blind Randomization Phase (Phase C). The double-blind treatment included either placebo-plus-ADT or aripiprazole-plus-ADT.

1.3 Statistical Issues and Findings

Study 138139 suggests a potential interaction between treatment and gender. From the subgroup analysis, aripiprazole does not seem to be effective for males. However, the treatment-by-gender interaction does not show in Study 138163. Given that two studies are not consistent on this matter and the sample size of males is relatively smaller than females, it remains inconclusive whether there exists the treatment-by-gender interaction at this stage.

The secondary endpoints other than the key secondary endpoint were analyzed without pre-specifying the multiple comparison procedure. Even some of these secondary endpoints are nominally significant, it is not clear how to interpret the results of these secondary endpoints as the conclusion will depend on the multiple testing procedure that one uses.

2. INTRODUCTION

2.1 Overview

The goal of this program was to evaluate ABILIFY® (aripiprazole) as adjunctive treatment in patients with major depressive disorder (MDD) who had not demonstrated an adequate response to antidepressant medication.

The MDD clinical efficacy program consisted of 3 placebo-controlled studies of identical design. Two studies, CN138139 and CN138163, have completed and one, CN138165, is ongoing. Patients entered a screening phase (Phase A) to assess eligibility and to allow for washout of prohibited concomitant medications. Eligible patients then entered an 8-week prospective treatment phase (Phase B), receiving single-blind placebo and 1 of 5 ADTs (escitalopram, sertraline, venlafaxine XR, fluoxetine, or paroxetine CR). If patients did not respond adequately to ADT treatment in Phase B, they were randomized to either aripiprazole-plus-ADT or placebo-plus-ADT in a 6-week randomization phase (Phase C).

2.2 Data Sources

The sponsor's electronic data is stored under the directory of \\CDSESUB1\N21436\S_018\2007-05-16 in the center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY 138139

3.1.1.1 Study Objectives

The primary objective of the study is to compare the efficacy of aripiprazole (2 to 20 mg/day) to placebo as adjunctive treatment to an assigned open-label marketed ADT in patients who demonstrated an incomplete response to a prospective 8-week trial of the same assigned open-label ADT.

3.1.1.2 Study Design

After the initial screening period of 7 to 28 days (Phase A), patients who met entrance criteria at the baseline visit (at the end of screening period) were enrolled into the 8-week Prospective Treatment Phase (Phase B) and were dispensed single-blind placebo plus an assigned open-label marketed ADT (placeboplus-ADT). The ADTs consisted of escitalopram (10 to 20 mg/day), fluoxetine (20 to 40 mg/day), either paroxetine (20 to 40 mg/day) or paroxetine CR (25 to 50 mg/day), sertraline (50 to 150 mg/day), or venlafaxine XR (37.5 to 225 mg/day).

Patients who completed Phase B and met criteria for an incomplete response were randomized into the 6-week double-blind Randomization Phase (Phase C) in a 1:1 ratio. An incomplete response was defined as a < 50% decrease in Hamilton Depression Rating Scale-Item 17 (HAM-D17) Total Score from the baseline visit to the end of Phase B (at Week 8 visit), a HAM-D17 Total Score ≥ 14 at the end of Phase B (Week 8 visit); and a Clinical Global Impression (CGI)-Improvement Score ≥ 3 at the end of Phase B (Week 8 visit).

The double-blind treatment included either placebo-plus-ADT (ie, double-blind placebo plus the same open-label ADT at a final dose reached during Phase B) or aripiprazole-plus-ADT (ie, double-blind aripiprazole plus the same open-label ADT as Phase B at a final dose reached during Phase B).

A total of 1044 patients were enrolled. 781 entered Phase B, 362 were randomized to Phase C with 178 to placebo and 184 to aripiprazole (2 patients who did not complete Phase B were randomized to aripiprazole in error).

3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary efficacy endpoint is the change from end of Phase B to end of Phase C (Week 14, LOCF) in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score.

(2) Secondary Efficacy Endpoints

The key secondary efficacy measure is the change from end of Phase B to Week 14 in the Sheehan Disability Scale (SDS) Mean Score.

Other secondary efficacy endpoints (all evaluated both LOCF and OC) are:

- Change from end of Phase B in MADRS Total Score to every study week in Phase C other than Week 14 (LOCF);
- Change from end of Phase B in MADRS Total Score to every study week in Phase C for the following two subgroups: those patients with < 25% improvement from baseline in MADRS Total Score at the end of Phase B, and those patients with ≥ 25% improvement from baseline in MADRS Total Score at the end of Phase B;

- Change from end of Phase B to every study week in Phase C in CGI Severity of Illness Score;
- Change from end of Phase B to every study week in Phase C in Inventory of Depressive Symptomatology Self-Report Scale (IDS-SR) Total Score;
- Change from end of Phase B to every study week in Phase C in Quick Inventory of Depressive Symptomatology Self-Report Scale (QIDS-SR) Total Score;
- CGI-Improvement Score at all study weeks in Phase C;
- Change from end of Phase B to Week 14 in HAM-D17 Total Score;
- MADRS Response at every study week in Phase C, where response is defined as ≥ 50% reduction in MADRS Total Score from end of Phase B;
- MADRS Partial Response at every study week in Phase C, where response is defined as ≥ 40% reduction in MADRS Total Score from end of Phase B;
- MADRS Remission at every study week in Phase C, where remission is defined by a MADRS Total Score of ≤ 10 and ≥ 50% reduction in MADRS Total Score from end of Phase B;
- CGI Improvement Response at every study week in Phase C where response is defined as a CGI-Improvement Score of 1 or 2 (very much improved or much improved);
- Change from Baseline (end of Phase A) in MADRS Total Score to every study week in Phase C;
- MADRS Response relative to Baseline at every study week in Phase C, where response is defined as ≥ 50% reduction in MADRS Total Score from end of Phase A.

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

Table 1. Disposition of Patients during Phase C in Study 138139

	Number of Patients (%)		
Patient Status	Placebo	Aripiprazole	Total
Randomized and Completed Phase B	178	182	360
Discontinued (a)	18 (10.1)	22 (12.1)	40 (11.1)
Lack of efficacy	2 (1.1)	2 (1.1)	4 (1.1)
Adverse event	4 (2.2)	6 (3.3)	10 (2.8)
Subject withdrew consent	4 (2.2)	5 (2.7)	9 (2.5)
Lost to follow up	4 (2.2)	5 (2.7)	9 (2.5)
Poor/Non-compliance	1 (0.6)	2 (1.1)	3 (0.8)
Subject no longer meets study criteria	3 (1.7)	1 (0.5)	4 (1.1)
Other known cause	0 (0.0)	1 (0.5)	1 (0.3)
Completed Phase C	160 (89.9)	160 (87.9)	320 (88.9)
Randomized in Error (b)	0	2	2

[Source: Sponsor's Clinical Study Report Table 5.1B]

Table 2. Demographic Characteristics in Study 138139

Variable		Placebo (N=178)	Aripiprazole (N=184)	Total (N=362)
Age (Years)	Mean	44.1	46.5	45.3
	Median	47.0	48.0	47.0
	Min-Max	21.0-64.0	21.0-65.0	21.0-65.0
	S.D.	10.9	10.6	10.8
Gender N(%)	Male	64 (36.0)	70 (38.0)	134 (37.0)
	Female	114 (64.0)	114 (62.0)	228 (63.0)
Race N(%)	White	165 (92.7)	161 (87.5)	326 (90.1)
	Black/African American	10 (5.6)	15 (8.2)	25 (6.9)
	Asian	0	3 (1.6)	3 (0.8)
	American Indian/Alaska Native	0	1 (0.5)	1 (0.3)
	Native Hawaiian/other Pacific islander	0	1 (0.5)	1 (0.3)
	Other	3 (1.7)	3 (1.6)	6 (1.7)
Ethnicity N(%)	Hispanic/Latino	13 (7.3)	6 (3.3)	19 (5.2)
	Not Hispanic/Latino	165 (92.7)	178 (96.7)	343 (94.8)

[Source: Sponsor's Clinical Study Report Table 5.3.1]

The baseline psychiatric characteristics of patients randomized to the aripiprazole and the placebo group were similar. The distribution of ADTs in the patient population in Phase C was also similar between the 2 treatment groups.

Table 3. Baseline Evaluation of Randomized Patients at the End of Phase B in Study 138139

		Placebo (N=178)	Aripiprazole (N=184)	Total (N=362)
HAM-D17 Total Score	Mean	19.9	19.7	19.8
	Median	20.0	19.0	19.0
	Min-Max	13.0-31.0	14.0-34.0	13.0-34.0
	S.D.	3.9	3.9	3.9
MADRS Total Score	Mean	26.0	26.0	26.0
	Median	25.0	26.0	25.0
	Min-Max	11.0-44.0	9.0-47.0	9.0-47.0
	S.D.	6.5	6.0	6.3
SDS Mean Score	Mean	5.5	5.8	5.7
	Median	5.7	6.0	5.7
	Min-Max	0.0-10.0	0.7-10.0	0.0-10.0
	S.D.	2.4	2.2	2.3
	Missing	0	2	2
CGI Severity of Illness Score	Mean	4.1	4.0	4.0
	Median	4.0	4.0	4.0
	Min-Max	3.0-6.0	3.0-6.0	3.0-6.0
	S.D.	0.6	0.6	0.6

[Source: Sponsor's Clinical Study Report Table 5.3.3]

3.1.1.5 Sponsor's Primary Efficacy Results

The mean change from end of Phase B to Week 14 (LOCF) on the MADRS Total Score is statistically significant with $p < 0.001$. The mean change from end of Phase B to Week 14 (LOCF) on the SDS Mean Score is not statistically significant between the treatment groups ($p = 0.055$).

Table 4. Primary and Key Secondary Efficacy Results in Study 138139

Variable	Double-Blind Treatment Group: Placebo	Double-Blind Treatment Group: Aripiprazole
PRIMARY EFFICACY ENDPOINT		
MADRS Total Score	N = 172	N = 181
Mean end of Phase B (SE)	25.65 (0.51)	25.88 (0.48)
Mean Change at Week 14 (SE)	-5.77 (0.67)	-8.78 (0.63)
Treatment Difference (95% CI) (a)		-3.01 (-4.66 , -1.37)
p-value		< 0.001
KEY SECONDARY EFFICACY ENDPOINT		
Sheehan Disability Scale Mean Score	N = 164	N = 167
Mean end of Phase B (SE)	5.35 (0.20)	5.69 (0.19)
Mean Change at Week 14 (SE)	-0.65 (0.19)	-1.11 (0.18)
Treatment Difference (95% CI) (a)		-0.46 (-0.93 , 0.01)
p-value		0.055

[Source: Sponsor's Clinical Study Report Table 7.1, verified by the reviewer]

Table 5. LOCF Analysis on Primary Endpoint by Week in Study 138139

		MADRS Total Score (a)								
		Placebo			Aripiprazole			Treatment Comparison (b) Aripiprazole - Placebo		
	Week	N	Mean	SE	N	Mean	SE	Difference	(95% CI)	p-value
End of Phase B		172	25.65	0.51	181	25.88	0.48	0.24	(-1.00 , 1.47)	0.707
Change from End of Phase B	9	164	-2.35	0.41	177	-3.19	0.38	-0.84	(-1.84 , 0.17)	0.101
	10	172	-3.39	0.51	181	-6.32	0.48	-2.93	(-4.18 , -1.69)	< 0.001
	11	172	-4.74	0.58	181	-7.95	0.54	-3.21	(-4.62 , -1.80)	< 0.001
	12	172	-4.92	0.62	181	-8.96	0.58	-4.04	(-5.54 , -2.54)	< 0.001
	13	172	-5.34	0.64	181	-9.44	0.60	-4.10	(-5.66 , -2.54)	< 0.001
	14	172	-5.77	0.67	181	-8.78	0.63	-3.01	(-4.66 , -1.37)	< 0.001

[Source: Sponsor's Clinical Study Report Table 7.2A]

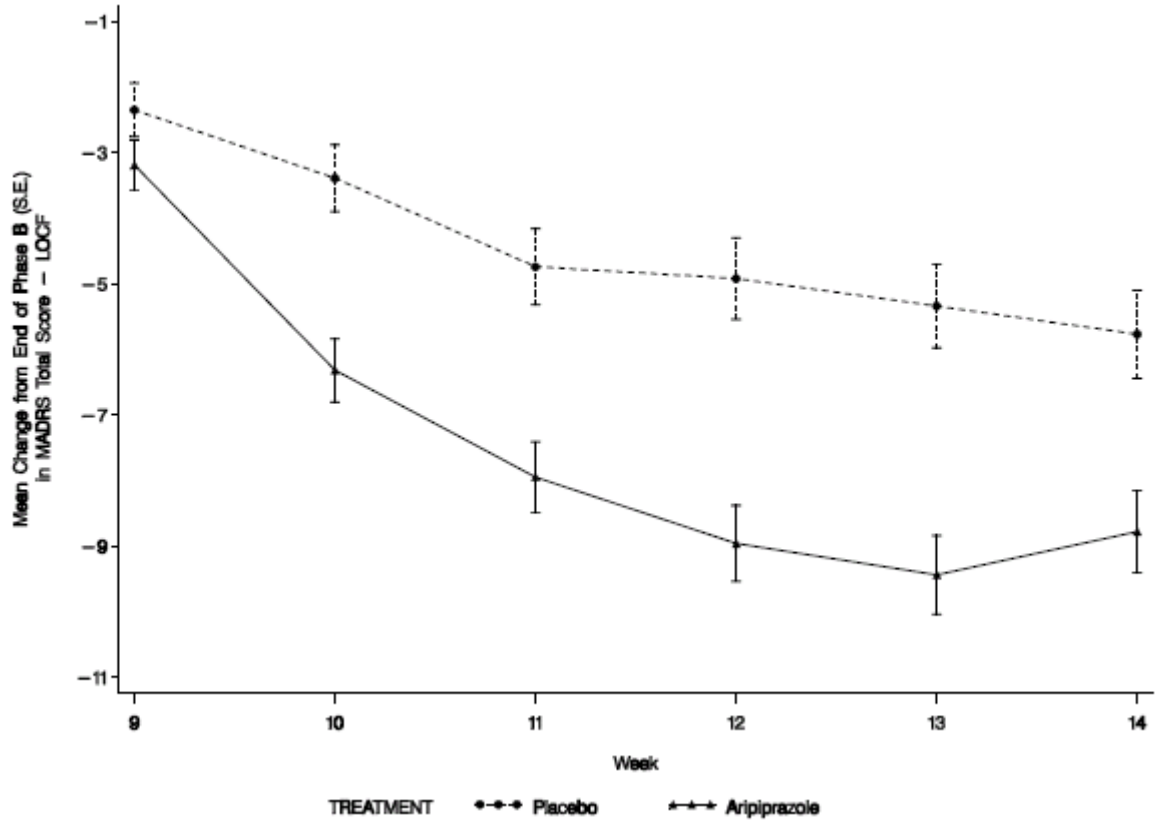
The sensitivity analyses by observed case analysis (OC analysis) on the total MADRS score shows consistent significant result. Figure 2 displays the adjusted mean change in MADRS score over time and the treatment effect appears to be stable within the 6-week trial period.

Table 6. OC Sensitivity Analysis of the Primary Endpoint in Study 138139

week	placebo			Aripiprazole					
	N	Mean	SE	N	Mean	SE	Difference	CI	p-value
9	164	-2.06	0.34	177	-2.85	0.4	-0.84	(-1.84, 0.17)	0.101
10	160	-3.15	0.46	168	-6.29	0.48	-3.09	(-4.38, -1.80)	<0.001
11	161	-4.64	0.54	161	-8.34	0.55	-3.65	(-5.14, -2.16)	<0.001
12	153	-4.81	0.56	156	-9.48	0.6	-4.77	(-6.37, -3.16)	<0.001
13	159	-5.33	0.61	154	-9.71	0.57	-4.48	(-6.12, -2.85)	<0.001
14	154	-6.04	0.63	154	-9.34	0.65	-3.16	(-4.90, -1.42)	<0.001

[Source: Reviewer's results. Reported p-values are not adjusted for multiplicity]

Figure 1. Adjusted Mean Change in MADRS Total Score by Week (LOCF)



[Source: Sponsor's Clinical Study Report Figure7.2A]

The weekly LOCF analysis and the OC sensitivity analysis by week are not performed on SDS since most patients only have SDS measurements in Week 8 and Week 14.

Table 7. OC Sensitivity Analysis of SDS at Week 14 in Study 138139

week	placebo			Aripiprazole					
	N	Mean	SE	N	Mean	SE	Difference	CI	p-value
14	153	-0.6	0.19	153	-1.21	0.2	-0.51	(-1.00, -0.03)	0.0394

[Source: Reviewer's results]

The medical reviewer is concerned about the considerable number of protocol violations in the study primarily due to usage of opiates/barbiturates. The number of patients with positive urine drug test appears to be balanced (25 in placebo and 26 in aripiprazole) in the study. The difference in the number of patients who used prohibited medications between the two groups are not negligible but not huge (15 in placebo and 10 in aripiprazole during Phase B, 13 in placebo and 16 in aripiprazole during Phase C). The sponsor conducted per protocol analysis excluding all protocol violations as well as excluding some patients with clinical meaningful violations as shown in Table 8 and Table 9. The statistical significance still holds for the total MADRS score but not any more for SDS score.

Table 8. Per Protocol Analysis on the Primary and Key Secondary Endpoints Excluding All Protocol Violations

		Placebo			Aripiprazole			Treatment Comparison[a] Aripiprazole - Placebo		
		N	Mean	SE	N	Mean	SE	Difference	(95% CI)	p-value
Study CN138139										
MADRS Total Score	End of Phase B	119	24.89	0.61	127	26.02	0.57	1.13	(-0.30, 2.55)	0.120
	Change from End of Phase B at Endpoint LOCF Week 14	119	-6.06	0.86	127	-9.07	0.79	-3.01	(-5.01, -1.00)	0.003
SDS Mean Score	End of Phase B	114	4.94	0.25	117	5.55	0.23	0.61	(0.03, 1.19)	0.038
	Change from End of Phase B at Endpoint LOCF Week 14	114	-0.72	0.26	117	-0.98	0.24	-0.26	(-0.87, 0.34)	0.393
Study CN138163										
MADRS Total Score	End of Phase B	142	26.34	0.53	122	24.76	0.58	-1.59	(-2.97, -0.20)	0.025
	Change from End of Phase B at Endpoint LOCF Week 14	142	-5.73	0.79	122	-8.25	0.87	-2.53	(-4.61, -0.45)	0.017
SDS Mean Score	End of Phase B	130	5.44	0.24	118	5.03	0.26	-0.42	(-1.01, 0.18)	0.173
	Change from End of Phase B at Endpoint LOCF Week 14	130	-0.92	0.23	118	-1.18	0.24	-0.26	(-0.82, 0.29)	0.348

[Source: Sponsor's Table 3.1 from the response to FDA requests on August 30, 2007]

Table 9. Analysis on the Primary and Key Secondary Endpoints Excluding Patients with Clinically Relevant Deviations

		Placebo			Aripiprazole			Treatment Comparison[a] Aripiprazole - Placebo		
		N	Mean	SE	N	Mean	SE	Difference	(95% CI)	p-value
Study CN138139										
MADRS Total Score	End of Phase B	153	25.83	0.55	162	25.90	0.51	0.07	(-1.26, 1.40)	0.918
	Change from End of Phase B at Endpoint LOCF Week 14	153	-5.69	0.72	162	-9.03	0.67	-3.34	(-5.08, -1.61)	<0.001
SDS Mean Score	End of Phase B	145	5.26	0.22	150	5.70	0.20	0.44	(-0.09, 0.96)	0.101
	Change from End of Phase B at Endpoint LOCF Week 14	145	-0.65	0.21	150	-1.08	0.19	-0.43	(-0.94, 0.08)	0.097
Study CN138163										
MADRS Total Score	End of Phase B	166	26.44	0.47	164	24.72	0.48	-1.72	(-2.90, -0.53)	0.005
	Change from End of Phase B at Endpoint LOCF Week 14	166	-5.73	0.72	164	-8.64	0.74	-2.91	(-4.74, -1.08)	0.002
SDS Mean Score	End of Phase B	152	5.44	0.21	159	5.10	0.22	-0.34	(-0.86, 0.18)	0.201
	Change from End of Phase B at Endpoint LOCF Week 14	152	-0.84	0.20	159	-1.39	0.20	-0.54	(-1.02, -0.06)	0.027

[Source: Sponsor's Table 3.2 from the response to FDA requests on August 30, 2007]

3.1.1.6 Sponsor's Secondary Efficacy Results

Table 10. Other Secondary Efficacy Results in Study 138139

Variable	Double-Blind Treatment Group: Placebo	Double-Blind Treatment Group: Aripiprazole
OTHER EFFICACY ENDPOINTS		
HAM-D17 Total Score	N = 147	N = 152
Mean end of Phase B (SE)	19.73 (0.36)	19.68 (0.34)
Mean Change at Week 14 (SE)	-4.89 (0.51)	-7.17 (0.48)
Treatment Difference (95% CI) (a)		-2.28 (-3.54 , -1.02)
p-value		< 0.001
CGI Improvement Score (Relative to Phase B)	N = 172	N = 181
Mean at Week 14 (SE)	2.81 (0.09)	2.49 (0.08)
Treatment Difference (95% CI) (a)		-0.32 (-0.53 , -0.11)
p-value		0.003
CGI Severity Score	N = 172	N = 181
Mean end of Phase B (SE)	4.11 (0.05)	4.08 (0.04)
Mean Change at Week 14 (SE)	-0.64 (0.08)	-1.03 (0.08)
Treatment Difference (95% CI) (a)		-0.39 (-0.59 , -0.18)
p-value		< 0.001
IDS-SR Total Score	N = 172	N = 181
Mean end of Phase B (SE)	34.04 (1.10)	34.43 (1.03)
Mean Change at Week 14 (SE)	-5.16 (0.81)	-6.95 (0.76)
Treatment Difference (95% CI) (a)		-1.79 (-3.77 , 0.19)
p-value		0.076
QIDS-SR Total Score	N = 172	N = 181
Mean end of Phase B (SE)	12.71 (0.42)	12.94 (0.40)
Mean Change at Week 14 (SE)	-2.28 (0.33)	-2.58 (0.31)
Treatment Difference (95% CI) (a)		-0.30 (-1.11 , 0.51)
p-value		0.470
Q-LES-Q Overall General Subscore	N = 161	N = 166
Mean end of Phase B (SE)	41.96 (1.39)	43.73 (1.31)
Mean Change at Week 14 (SE)	6.87 (1.15)	9.20 (1.08)
Treatment Difference (95% CI) (a)		2.33 (-0.49 , 5.15)
p-value		0.106
MADRS Response Rate (>=50% Reduction from End of Phase B in MADRS Total Score)	N = 172	N = 181
Proportion(%) of Responders at Week 14	41 (23.8%)	61 (33.7%)
RR (95% CI) (b)		1.45 (1.04 , 2.01)
p-value		0.027

Variable	Double-Blind Treatment Group: Placebo	Aripiprazole
MADRS Partial Response Rate (>=40% Reduction from End of Phase B in MADRS Total Score)	N = 172	N = 181
Proportion(%) of Responders at Week 14	48 (27.9%)	80 (44.2%)
RR (95% CI) (b)		1.60 (1.20 , 2.13)
p-value		0.001
MADRS Remission Rate (MADRS Total Score <=10, and >=50% Reduction from End of Phase B)	N = 172	N = 181
Proportion(%) of Remitters at Week 14	27 (15.7%)	47 (26.0%)
RR (95% CI) (b)		1.70 (1.13 , 2.56)
p-value		0.011
CGI Improvement Response Rate (response defined as 'very much improved' or 'much improved' relative to End of Phase B)	N = 172	N = 181
Proportion(%) of Responders at Week 14	64 (37.2%)	96 (53.0%)
RR (95% CI) (b)		1.44 (1.14 , 1.81)
p-value		0.002
OTHER SECONDARY ENDPOINTS BASED ON BASELINE ASSESSMENTS		
MADRS Total Score	N = 172	N = 181
Mean Baseline (SE)	30.00 (0.36)	31.42 (0.34)
Mean Change at Week 14 (SE)	-10.49 (0.77)	-14.04 (0.72)
Treatment Difference (95% CI) (a)		-3.55 (-5.44 , -1.67)
p-value		< 0.001
MADRS Response Rate (>=50% Reduction from Baseline in MADRS Total Score)	N = 172	N = 181
Proportion(%) of Responders at Week 14	55 (32.0%)	87 (48.1%)
RR (95% CI) (b)		1.52 (1.17 , 1.97)
p-value		0.001

[Source: Sponsor's Clinical Study Report Table 7.1]

3.1.1.7 Reviewer's Results

The reviewer validated the sponsor's results on the primary and the key secondary endpoints. Comparing with the sponsor's results, the results from the reviewer have small differences in some other secondary endpoints, such as CGI improvement score, CGI severity score and HAM-D17 total score shown in Table 11. The difference does not affect the conclusions of the secondary endpoints. The sponsor did not pre-specify any multiple testing procedures for these additional secondary endpoints so it is not clear how to interpret the results of these secondary endpoints as the conclusion will depend on the multiple testing procedure that one uses.

Table 11. Some Secondary Efficacy Results in Study 138139 from the Reviewer

	Placebo		Aripiprazole		
	mean at Phase B	mean change	mean at Phase B	mean change	p-value
HAM-D17	19.78	-4.86	19.63	-7.14	0.0005
CGI Severity Score	4.43	-0.97	4.54	-1.43	<0.0001
Q-LES-Q	42.08	6.87	43.8	9.2	0.106
CGI improvement	2.85 (mean at Phase C)		2.51 (mean at Phase C)		0.0025

[Source: Reviewer's results. Reported p-values are not adjusted for multiplicity]

3.1.1.8 Conclusions

The primary endpoint, mean change from end of Phase B to Week 14 (LOCF) on the MADRS Total Score, is statistically significant with $p < 0.001$ in the trial. Aripiprazole is able to demonstrate the treatment effect on mean change in MADRS Total Score from Week 10 and beyond. The key secondary endpoint is on the borderline with $p=0.055$. Even though most of other secondary endpoints are nominally significant, it is hard to interpret since no multiple testing procedure was pre-specified.

3.1.2 STUDY CN138163

This study has identical design and objective with the other study CN138139. For more details, please refer to section 3.1.1.

3.1.2.1 Study Objectives

The primary objective is to compare the efficacy of aripiprazole to placebo as adjunctive treatment to an assigned open-label marketed ADT in patients with incomplete response at Week 8.

3.1.2.2 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study. Patients who had an incomplete response at the end of Week 8 were randomized into the 6-week double-blind Randomization Phase (Phase C) in a 1:1 ratio. An incomplete response was defined as a < 50% decrease in Hamilton Depression Rating Scale-Item 17 (HAM-D17) Total Score from the baseline to Week 8 visit. A total of 1151 patients were enrolled. 830 entered Phase B, 381 were randomized to Phase C with 190 to placebo and 191 to aripiprazole).

3.1.2.3 Efficacy Measures

(1) <u>Primary Efficacy Endpoint</u>

The primary efficacy endpoint is the mean change from end of Phase B (Week 8) to Week 14 on the MADRS Total Score.

(2) Secondary Efficacy Endpoints

The key secondary efficacy measure is the change from end of Phase B to Week 14 in the SDS Mean Score.

Other secondary endpoints are same as in Study CN 138139.

3.1.2.4 Patient Disposition, Demographic and Baseline Characteristics

Table 12. Disposition of Patients during Phase C in Study 138163

	Number of Patients (%)		
Patient Status	Placebo	Aripiprazole	Total
Randomized and Completed Phase B	190	191	381
Discontinued (a)	28 (14.7)	29 (15.2)	57 (15.0)
Lack of efficacy	3 (1.6)	4 (2.1)	7 (1.8)
Adverse event	2 (1.1)	7 (3.7)	9 (2.4)
Subject withdrew consent	10 (5.3)	3 (1.6)	13 (3.4)
Lost to follow up	7 (3.7)	5 (2.6)	12 (3.1)
Poor/Non-compliance	2 (1.1)	2 (1.0)	4 (1.0)
Subject no longer meets study criteria	4 (2.1)	7 (3.7)	11 (2.9)
Other known cause	0 (0.0)	1 (0.5)	1 (0.3)
Completed Phase C	162 (85.3)	162 (84.8)	324 (85.0)

[Source: Sponsor's Clinical Study Report Table 5.1B]

Table 13. Demographic Characteristics of Randomized Patients in Study 138163

Variable		Placebo (N=190)	Aripiprazole (N=191)	Total (N=381)
Age (Years)	Mean	44.4	44.6	44.5
	Median	44.5	45.0	45.0
	Min-Max	20.0-66.0	19.0-67.0	19.0-67.0
	S.D.	10.7	11.0	10.8
Gender N(%)	Male	62 (32.6)	65 (34.0)	127 (33.3)
	Female	128 (67.4)	126 (66.0)	254 (66.7)
Race N(%)	White	169 (88.9)	170 (89.0)	339 (89.0)
	Black/African American	14 (7.4)	14 (7.3)	28 (7.3)
	Asian	4 (2.1)	3 (1.6)	7 (1.8)
	American Indian/Alaska Native	1 (0.5)	1 (0.5)	2 (0.5)
	Native Hawaiian/other Pacific islander	0	1 (0.5)	1 (0.3)
	Other	2 (1.1)	2 (1.0)	4 (1.0)
Ethnicity N(%)	Hispanic/Latino	18 (9.5)	11 (5.8)	29 (7.6)
	Not Hispanic/Latino	172 (90.5)	180 (94.2)	352 (92.4)

[Source: Sponsor's Clinical Study Report Table 5.3.1]

Table 14. Baseline Characteristics at the End of Phase B for Randomized Patients in Study 138163

		Placebo (N=190)	Aripiprazole (N=191)	Total (N=381)
HAM-D17 Total Score	Mean	20.0	19.2	19.6
	Median	20.0	19.0	19.0
	Min-Max	14.0-31.0	14.0-31.0	14.0-31.0
	S.D.	3.8	3.9	3.9
MADRS Total Score	Mean	27.0	25.2	26.1
	Median	27.0	25.0	26.0
	Min-Max	15.0-42.0	11.0-41.0	11.0-42.0
	S.D.	5.5	6.2	5.9
SDS Mean Score	Mean	5.5	5.2	5.3
	Median	5.7	5.3	5.3
	Min-Max	0.0-10.0	0.0-10.0	0.0-10.0
	S.D.	2.2	2.4	2.3
	Missing	1	0	1
CGI Severity of Illness Score	Mean	4.1	4.0	4.1
	Median	4.0	4.0	4.0
	Min-Max	3.0-6.0	3.0-6.0	3.0-6.0
	S.D.	0.6	0.6	0.6
IDS-Self Rated Total Score	Mean	33.1	30.9	32.0
	Median	33.0	29.0	31.0
	Min-Max	4.0-60.0	2.0-65.0	2.0-65.0
	S.D.	11.5	12.0	11.8
QIDS-SR Total Score	Mean	12.6	11.8	12.2
	Median	13.0	12.0	12.0
	Min-Max	1.0-23.0	0.0-23.0	0.0-23.0
	S.D.	4.5	4.5	4.5

[Source: Sponsor's Clinical Study Report Table 5.3.3]

3.1.2.5 Sponsor's Primary Efficacy Results

The mean change from end of Phase B to Week 14 (LOCF) in the MADRS Total Score is statistically significant with p=0.001. The key secondary endpoint mean change of SDS Score from end of Phase B is also statistically significant with p-value of 0.012. The OC sensitivity analysis on the total MADRS score by week is listed in Table 17. Figure 2 displays the adjusted mean change in MADRS score over time and the treatment effect appears to be stable within the 6-week trial.

Table 15. Primary and Key Secondary Results in Study 138163

Variable	Double-Blind Treatment Group: Placebo	Double-Blind Treatment Group: Aripiprazole
PRIMARY EFFICACY ENDPOINT		
MADRS Total Score	N = 184	N = 185
Mean end of Phase B (SE)	26.55 (0.44)	24.59 (0.44)
Mean Change at Week 14 (SE)	-5.65 (0.64)	-8.49 (0.66)
Treatment Difference (95% CI) (a)		-2.84 (-4.53 , -1.15)
p-value		0.001
KEY SECONDARY EFFICACY ENDPOINT		
Sheehan Disability Scale Mean Score	N = 168	N = 180
Mean end of Phase B (SE)	5.35 (0.19)	5.06 (0.19)
Mean Change at Week 14 (SE)	-0.73 (0.18)	-1.31 (0.17)
Treatment Difference (95% CI) (a)		-0.57 (-1.02 , -0.13)
p-value		0.012

[Source: Sponsor's Clinical Study Report Table 7.1, verified by the reviewer]

Table 16. LOCF Analysis of Primary Endpoint by Week in Study 138163

		MADRS Total Score (a)								
		Placebo			Aripiprazole			Treatment Comparison (b) Aripiprazole - Placebo		
	Week	N	Mean	SE	N	Mean	SE	Difference	(95% CI)	p-value
End of Phase B		184	26.55	0.44	185	24.59	0.44	-1.95	(-3.10 , -0.81)	< 0.001
Change from End of Phase B	9	174	-2.18	0.43	173	-3.71	0.43	-1.54	(-2.65 , -0.43)	0.007
	10	184	-3.43	0.53	185	-6.60	0.53	-3.18	(-4.56 , -1.80)	< 0.001
	11	184	-4.79	0.56	185	-7.65	0.57	-2.86	(-4.33 , -1.39)	< 0.001
	12	184	-5.58	0.61	185	-8.43	0.62	-2.85	(-4.46 , -1.25)	< 0.001
	13	184	-5.72	0.63	185	-8.79	0.64	-3.07	(-4.73 , -1.41)	< 0.001
	14	184	-5.65	0.64	185	-8.49	0.66	-2.84	(-4.53 , -1.15)	0.001

[Source: Sponsor's Clinical Study Report Table 7.2A]

Table 17. OC Sensitivity Analysis of Primary Endpoint in Study 138163

week	placebo			Aripiprazole					
	N	Mean	SE	N	Mean	SE	Difference	CI	p-value
9	174	-2.38	0.39	173	-3.51	0.41	-1.54	(-2.65, -0.43)	0.007
10	168	-3.73	0.52	177	-6.86	0.51	-3.25	(-4.68, -1.81)	<0.001
11	162	-4.86	0.55	168	-7.95	0.58	-3.19	(-4.77, -1.61)	<0.001
12	158	-6.15	0.6	165	-8.53	0.6	-2.8	(-4.52, -1.09)	0.001
13	154	-6.14	0.67	163	-8.85	0.63	-2.94	(-4.77, -1.12)	0.001
14	161	-6.23	0.64	164	-9.05	0.65	-3.06	(-4.89, -1.24)	0.001

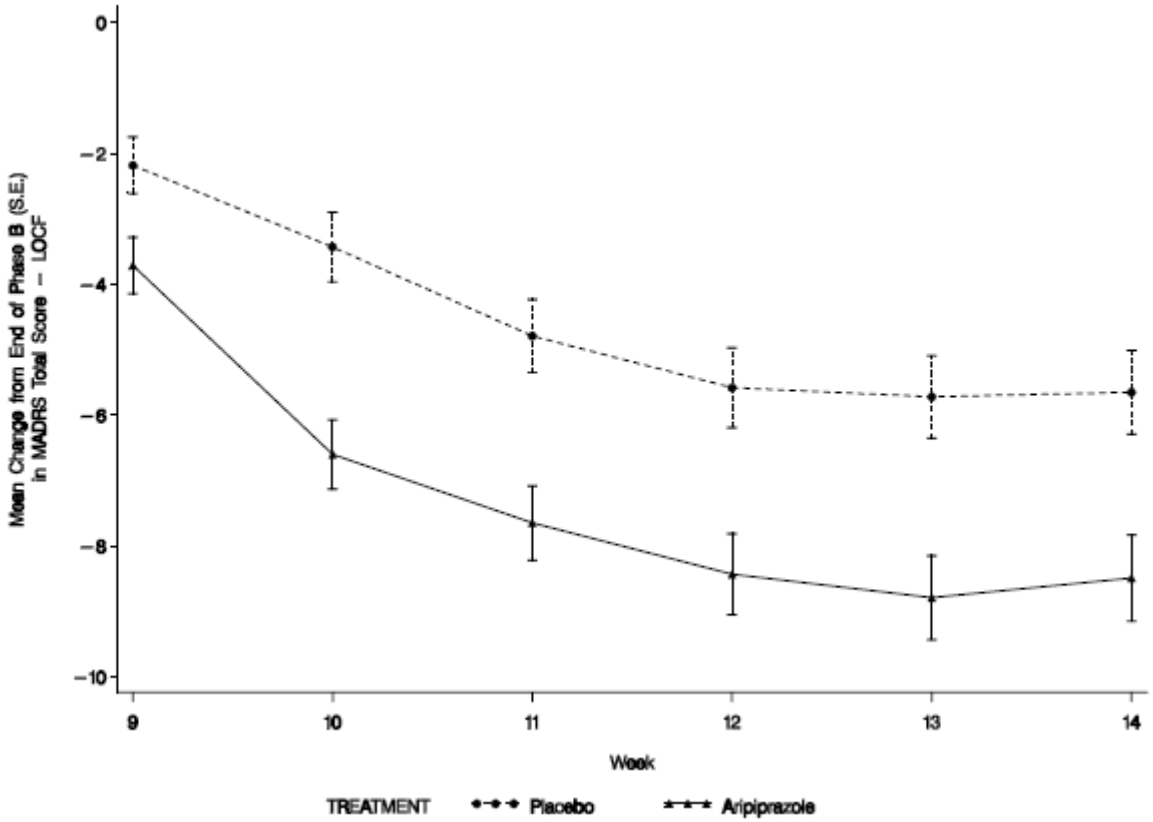
[Source: Reviewer's results. Reported p-values are not adjusted for multiplicity]

Table 18. OC Sensitivity Analysis of SDS at Week 14 in Study 138163

week	placebo			Aripiprazole					
	N	Mean	SE	N	Mean	SE	Difference	CI	p-value
14	155	-0.71	0.19	162	-1.29	0.17	-0.62	(-1.08, -0.16)	0.009

[Source: Reviewer's results.]

Figure 2. Adjusted Mean Change in MADRS Total Score by Week (LOCF)



[Source: Sponsor's Clinical Study Report]

The number of patients with positive urine drug test appears to be balanced (21 in placebo and 20 in aripiprazole). The difference of patients who used prohibited medications between the two groups are huge during Phase C (12 in placebo and 14 in aripiprazole during Phase B, 9 in placebo and 24 in aripiprazole during Phase C). The sponsor conducted per protocol analysis excluding all protocol violations as well as excluding some patients with clinical meaningful violations as shown in Table 8 and Table 9. The results no longer show statistical significance. However, it is difficult to interpret, partially because the analyses are conducted post hoc. The randomization principle in clinical trial can be violated when the analyses are performed post hoc. Also the implication of excluding protocol violation (majority of them because of positive urine drug test) in the analysis is not clear since the post-approval population can have the same inclination for drug use.

3.1.2.6 Sponsor's Secondary Efficacy Results

Table 19. Secondary Efficacy Results of Study CN138163

Variable	Double-Blind Treatment Group: Placebo	Double-Blind Treatment Group: Aripiprazole
OTHER EFFICACY ENDPOINTS		
HAM-D17 Total Score	N = 170	N = 181
Mean end of Phase B (SE)	19.64 (0.29)	18.75 (0.29)
Mean Change at Week 14 (SE)	-4.41 (0.48)	-6.77 (0.48)
Treatment Difference (95% CI) (a)		-2.35 (-3.60 , -1.11)
p-value		< 0.001
CGI Improvement Score (Relative to Phase B)	N = 184	N = 185
Mean at Week 14 (SE)	2.91 (0.08)	2.42 (0.08)
Treatment Difference (95% CI) (a)		-0.49 (-0.70 , -0.28)
p-value		< 0.001
CGI Severity Score	N = 184	N = 185
Mean end of Phase B (SE)	4.07 (0.04)	4.02 (0.04)
Mean Change at Week 14 (SE)	-0.63 (0.08)	-1.10 (0.08)
Treatment Difference (95% CI) (a)		-0.48 (-0.68 , -0.27)
p-value		< 0.001
IDS-SR Total Score	N = 184	N = 187
Mean end of Phase B (SE)	32.34 (0.94)	30.27 (0.93)
Mean Change at Week 14 (SE)	-4.55 (0.73)	-6.03 (0.73)
Treatment Difference (95% CI) (a)		-1.47 (-3.36 , 0.42)
p-value		0.126
QIDS-SR Total Score	N = 184	N = 187
Mean end of Phase B (SE)	12.33 (0.36)	11.60 (0.36)
Mean Change at Week 14 (SE)	-1.80 (0.31)	-2.30 (0.30)
Treatment Difference (95% CI) (a)		-0.50 (-1.29 , 0.29)
p-value		0.213
Q-LES-Q Overall General Subscore	N = 170	N = 181
Mean end of Phase B (SE)	44.38 (1.16)	47.19 (1.13)
Mean Change at Week 14 (SE)	4.85 (1.13)	9.00 (1.11)
Treatment Difference (95% CI) (a)		4.15 (1.26 , 7.05)
p-value		0.005
MADRS Response Rate (>=50% Reduction from End of Phase B in MADRS Total Score)	N = 184	N = 185
Proportion(%) of Responders at Week 14	32 (17.4%)	60 (32.4%)
RR (95% CI) (b)		1.86 (1.27 , 2.71)
p-value		< 0.001
MADRS Partial Response Rate (>=40% Reduction from End of Phase B in MADRS Total Score)	N = 184	N = 185
Proportion(%) of Responders at Week 14	44 (23.9%)	79 (42.7%)
RR (95% CI) (b)		1.75 (1.30 , 2.37)
p-value		< 0.001
MADRS Remission Rate (MADRS Total Score <=10, and >=50% Reduction from End of Phase B)	N = 184	N = 185
Proportion(%) of Remitters at Week 14	28 (15.2%)	47 (25.4%)
RR (95% CI) (b)		1.66 (1.09 , 2.54)
p-value		0.016
CGI Improvement Response Rate (response defined as 'very much improved' or 'much improved' relative to End of Phase B)	N = 184	N = 185
Proportion(%) of Responders at Week 14	57 (31.0%)	104 (56.2%)
RR (95% CI) (b)		1.76 (1.38 , 2.25)
p-value		< 0.001
OTHER SECONDARY ENDPOINTS BASED ON BASELINE ASSESSMENTS		
MADRS Total Score	N = 184	N = 187
Mean Baseline (SE)	30.77 (0.35)	30.34 (0.35)
Mean Change at Week 14 (SE)	-9.92 (0.71)	-14.10 (0.72)
Treatment Difference (95% CI) (a)		-4.18 (-6.02 , -2.34)
p-value		< 0.001
MADRS Response Rate (>=50% Reduction from Baseline in MADRS Total Score)	N = 184	N = 185
Proportion(%) of Responders at Week 14	44 (23.9%)	83 (44.9%)
RR (95% CI) (b)		1.82 (1.35 , 2.45)
p-value		< 0.001

3.1.2.7 Reviewer's Results

The primary and key secondary efficacy results from the reviewer are the same as ones provided by the sponsor. The reviewer has small differences in some of the additional secondary endpoints shown in Table 20 compared with the sponsor's. However, the difference does not affect the conclusions of the additional secondary endpoints. The sponsor did not pre-specify any multiple testing procedures. Therefore, it is not clear how to interpret the results of these secondary endpoints as it will depend on the multiple testing procedure that one uses.

Table 20. Some Secondary Efficacy Results in Study 138163 from the Reviewer

	Placebo		Aripiprazole		
	mean at Phase B	mean change	mean at Phase B	mean change	p-value
HAM-D17	19.74	-4.31	18.79	-6.78	0.0001
CGI Severity Score	4.41	-0.97	4.4	-1.47	<0.0001
IDS-SR	32.23	-4.57	29.81	-6.17	0.0986
QIDS-SR	12.3	-1.82	11.48	-2.38	0.163
Q-LES-Q	44.21	4.87	47.08	8.97	0.006
CGI improvement	2.92 (mean at Phase C)		2.40 (mean at phase C)		<0.0001

[Source: Reviewer's results. Reported p-values are not adjusted for multiplicity]

3.1.2.8 Conclusions

Both the primary endpoint and the key secondary endpoint are statistically significant with p-values of less than 0.01 and 0.012, respectively. Aripiprazole is able to demonstrate the significant treatment effect on mean change in MADRS Total Score from Week 9. Even though a number of other secondary endpoints are nominally significant, it is hard to interpret since no multiple testing procedure was pre-specified.

3.2 Evaluation of Safety

The evaluation of safety is not performed in this report. Please refer the clinical review of this application for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Study 138139 suggests an interaction between treatment and gender. From the subgroup analysis, aripiprazole does not seem to be numerically better than placebo for males. However, the treatment-by-gender interaction does not exist in Study 138163. Given that two studies are not consistent on this matter and the sample size of males is relatively smaller than females, it may be too assertive to conclude the existence of the treatment-by-gender interaction at this stage.

Table 21. Subgroup analyses in Study 138139

	placebo			aripiprazole		
	N	Mean	STD	N	Mean	STD
male	60	-7.18	6.67	70	-6.96	8.11
female	112	-5.17	8.02	111	-10.04	7.94
white	159	-5.57	7.68	159	-9.04	8.05
non-white	13	-9.61	5.77	22	-7.45	8.75
age<50	110	-5.43	7.19	101	-8.48	8.32
age>=50	62	-6.65	8.32	80	-9.33	7.9

[Source: reviewer's results]

Table 22. Subgroup analyses in Study 138163

	Placebo			Aripiprazole		
	N	Mean	STD	N	Mean	STD
Male	59	-5.39	7.40	62	-6.95	8.57
Female	125	-5.90	8.36	123	-9.03	8.26
White	165	-5.95	8.16	164	-8.20	8.30
Non-White	19	-3.89	6.92	21	-9.38	9.35
Age<50	122	-5.60	7.96	120	-8.18	8.72
Age>=50	62	-6.02	8.28	65	-8.63	7.84

[Source: reviewer's results]

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study 138139 suggests a potential interaction between treatment and gender. From the subgroup analysis, aripiprazole does not seem to be effective for males. However, the treatment-by-gender interaction does not show in Study 138163. Given that two studies are not consistent on this

matter and the sample size of males is relatively smaller than females, it remains inconclusive whether there exists the treatment-by-gender interaction at this stage.

The secondary endpoints other than the key secondary endpoint were analyzed without pre-specifying the multiple comparison procedure. Even some of these secondary endpoints are nominally significant, it is not clear how to interpret the results of these secondary endpoints as the conclusion will depend on the multiple testing procedure that one uses.

5.2 Conclusions and Recommendations

The two identical placebo-controlled clinical trials support the efficacy claim of aripiprazole as an adjunct to antidepressants in treating patients with Major Depression Disorder (MDD).

The primary endpoint, mean change from end of Phase B to Week 14 (LOCF) in the MADRS Total Score, is statistically significant in both trials. The key secondary endpoint is on the borderline in Study 138139 but statistically significant in Study 138163. The reviewer found a potential interaction between treatment and gender in Study 138139. However, the treatment-by-gender interaction does not show in Study 138163. Given that two studies are not consistent on this matter and the sample size of males is relatively smaller than females in Study 138139, it remains inconclusive whether there exists the treatment-by-gender interaction at this stage.

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Jialu Zhang, Ph.D.

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/s/

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