25 April 2013
EMA/488884/2013
Committee for Medicinal Products for Human Use (CHMP)

Abilify

International non-proprietary name: Aripiprazole

Procedure no.: EMA/H/C/000471/P46 - 065

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

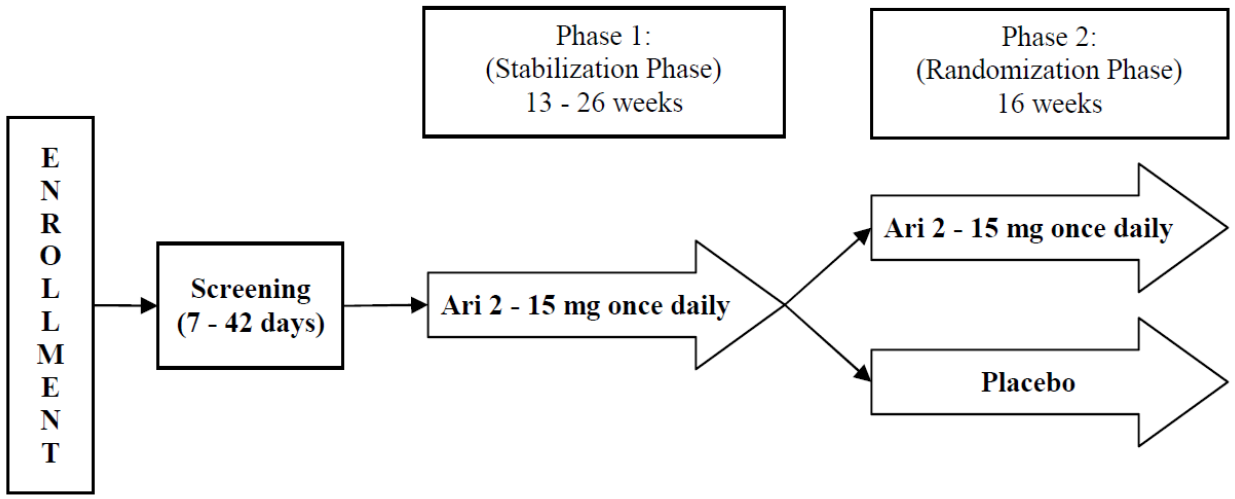
I. ASSESSMENT

Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:
results of the final clinical study report (CSR) for Study CN138603.1
Study CN138603 was a United States Food and Drug Administration post-approval commitment designed to assess whether paediatric subjects who maintained a response for 12 weeks of aripiprazole treatment for their symptoms of irritability associated with autistic disorder would experience a relapse significantly later when continuing therapy with aripiprazole than subjects treated with placebo.

Methodology
This was a multicenter, double-blind, randomized, placebo-controlled study with 2 parallel treatment groups designed to assess the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric subjects with irritability associated with autistic disorder. The study included 2 phases: Phase 1 (stabilization phase) - 13 - 26 weeks of single-blind aripiprazole treatment and Phase 2 (randomization phase) - 16 weeks of double-blind treatment with aripiprazole or placebo.
The study design is presented graphically in Figure below:

Figure 4.1: Study Design



The population included male or female subjects 6 to 17 years of age at the time of the baseline visit meeting DSM-IV-TR diagnostic criteria for autistic disorder and demonstrating behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. The diagnosis of autistic disorder was to be confirmed by the Autism Diagnostic Interview-Revised. Subjects were to have Clinical Global Impressions-Severity(CGI-S) scores ≥ 4 AND an Aberrant Behavior Checklist-Irritability (ABC-I) Subscale score ≥ 18 at the screening and baseline visits and to have a mental age of at least 24 months, as assessed by the investigators. A total of 215 subjects were enrolled in the study, and 157 (73%) completed the screening phase and entered Phase 1. Eighty-five subjects (54%) completed Phase 1 and were randomized in Phase 2 (41 and 44 in the aripiprazole and placebo groups, respectively).

Objectives
The primary objective was to evaluate the efficacy of aripiprazole compared with placebo to prevent relapses in pediatric subjects who maintained a response for 12 weeks of aripiprazole treatment for their symptoms of irritability associated with autistic disorder as measured by the time from randomization to relapse.
Secondary objectives of the study were:

- To evaluate the long-term effect of aripiprazole on the mean change from end of Phase 1 to endpoint on the Irritability subscale of the ABC-I score
- To evaluate the long-term effect of aripiprazole on the mean Clinical Global Impressions-Improvement Scale (CGI-I) score at endpoint

Statistical Considerations

The analysis populations included the following:

- The Enrolled Sample comprised all subjects who signed informed consent.
- The Phase 1 Safety Sample comprised all subjects who took at least 1 dose of single-blind aripiprazole in Phase 1 (Stabilization Phase), as indicated on the study therapy form.
- The Phase 1 Efficacy Sample comprised all subjects who were in the Phase 1 Safety Sample and had at least 1 efficacy evaluation after the start of Phase 1 study drug.
- The Randomized Sample comprised all subjects who were randomized in Phase 2 (Randomization Phase).
- The Phase 2 Safety Sample comprised all subjects in the Randomized Sample who took at least 1 dose of double-blind medication in Phase 2, as indicated on the study therapy form.
- The Phase 2 Efficacy Sample comprised all subjects who were in the Phase 2 Safety Sample and had at least 1 efficacy evaluation after the start of Phase 2 study drug.

Analysis Data Sets:

- The last observation carried forward (LOCF) data set included data recorded at a given visit or, if no observation was recorded at that visit, data carried forward from the previous visit.
- Baseline data of either Phase 1 or Phase 2 was not carried forward or averaged with on treatment data to impute missing values for the LOCF data set.
- The Observed Case (OC) data set consisted of the actual observation at each visit.

The LOCF data set was the primary data set. The analyses of the OC data set were considered secondary, and were performed to corroborate those analyses on the LOCF data set.

The primary efficacy outcome measure was the time from randomization to relapse. A total of 30 relapses would have provided 80% power to detect a significant difference in time to relapse between the 2 treatment groups using the log-rank test. This assumed a relapse rate of 25% in the aripiprazole group, a relapse rate of 55% in the placebo group, and a 2-sided alpha level of 0.05.

The hazard ratio for these assumed relapse rates was 0.36.

The primary efficacy outcome measure above was evaluated by a survival analysis using the Randomized Sample. The survivorship function and estimated survivorship curves were obtained from Kaplan-Meier estimates. Survival distributions of the 2 treatment groups were compared using the log-rank test, stratified by baseline body weight (2 categories: $\geq$ 40 kg and < 40 kg). The estimated hazard ratio and 95% confidence interval (CI) was obtained from the Cox regression model, with baseline body weight (2 categories: $\geq$ 40 kg and < 40 kg) as a stratification factor and with treatment group as a covariate.

The secondary outcome measures were mean change from baseline (end of Phase 1) to Week 16 endpoint (LOCF) in the ABC-I, and mean CGI-I score at Week 16 endpoint (LOCF). The mean change from baseline in the Irritability Subscale score was evaluated using analysis of covariance (ANCOVA) model that included the end of Phase 1 Irritability score as covariate, and treatment and baseline body weight (2 categories: $\geq$ 40 kg and < 40 kg) as main effects.

The mean CGI-I score was evaluated using an ANCOVA model, with CGI-S end of Phase 1 score as covariate and treatment and baseline body weight (2 categories: $\geq$ 40 kg and < 40 kg) as main effects.

Analysis of the secondary efficacy measures was performed on the Phase 2 Efficacy Sample, and was repeated utilizing the OC data set.

For the analysis of the secondary outcome measures, a hierarchical testing procedure was used in order for the overall experiment-wise type I error rate to be kept at $\leq$ 0.05.

Disposition

A total of 215 subjects were enrolled in the study, and 157 (73%) completed the screening phase and entered Phase 1 (Table below). Eighty-five subjects (54%) completed Phase 1 and were randomized in Phase 2 (41 and 44 in the aripiprazole and placebo groups, respectively).
Overall, 54% and 43% of aripiprazole and placebo subjects, respectively, completed Phase 2, and the most common reason for discontinuation was lack of efficacy in both treatment groups.

Patient Status	Placebo	Aripiprazole	Total
ENROLLED	-	-	215
SCREEN FAILURE OR DISCONTINUED DURING SCREENING PHASE (a)	-	-	58 (27.0)
ADVERSE EVENT	-	-	1 (0.5)
SUBJECT WITHDREW CONSENT	-	-	12 (5.6)
LOST TO FOLLOW-UP	-	-	8 (3.7)
SUBJECT NO LONGER MEETS STUDY CRITERIA	-	-	36 (16.7)
OTHER	-	-	1 (0.5)
COMPLETED SCREENING PHASE AND ENTERED PHASE 1 (a)	-	-	157 (73.0)
DISCONTINUED DURING PHASE 1 (b)	-	72 (45.9)	72 (45.9)
ADVERSE EVENT	-	12 (7.6)	12 (7.6)
SUBJECT WITHDREW CONSENT	-	7 (4.5)	7 (4.5)
LOST TO FOLLOW-UP	-	8 (5.1)	8 (5.1)
ADMINISTRATIVE REASON BY SPONSOR	-	11 (7.0)	11 (7.0)
SUBJECT NO LONGER MEETS STUDY CRITERIA	-	7 (4.5)	7 (4.5)
LACK OF EFFICACY	-	25 (15.9)	25 (15.9)
POOR/NON-COMPLIANCE	-	2 (1.3)	2 (1.3)
COMPLETED PHASE 1 (b)	-	85 (54.1)	85 (54.1)
RANDOMIZED	44	41	85
DISCONTINUED DURING PHASE 2 (c)	25 (56.8)	19 (46.3)	44 (51.8)
ADVERSE EVENT	1 (2.3)	0	1 (1.2)
SUBJECT WITHDREW CONSENT	0	5 (12.2)	5 (5.9)
LOST TO FOLLOW-UP	0	1 (2.4)	1 (1.2)
LACK OF EFFICACY	23 (52.3)	13 (31.7)	36 (42.4)
POOR/NON-COMPLIANCE	1 (2.3)	0	1 (1.2)
COMPLETED PHASE 2 (c)	19 (43.2)	22 (53.7)	41 (48.2)

Source: Table 4.2.1 of the CN138603 final CSR
(a) Percentages are based on the number of patients enrolled.
(b) Percentages are based on the number of patients completed Screening Phase and entered Phase 1 (Stabilization Phase).
(c) Percentages are based on the number of patients randomized using the randomized treatment.

Demographics

Demographic characteristics for the randomized sample were comparable across treatment groups (Table 4.3-1). The majority of subjects were male and White, and the median age was 10 years.

Baseline Disease Characteristics

In the Phase 1 safety sample, 81.3% of subjects were ≤ 12 years of age, 79.4% were male, and 69.0% were White.

Psychiatric evaluation of the randomized sample: at baseline, overall mean ABC Irritability, Hyperactivity, Stereotypy, Social Withdrawal, and Inappropriate Speech Scores appeared to be slightly higher in the aripiprazole group than in the placebo group. Mean CGI-S Scores were similar in both groups. In the Randomization Sample, the mean (median) time in stabilization was 135.0 (129.0) days and 125.3 (125.5) days in the aripiprazole and placebo groups, respectively:

Table 4.3-1: Demographic Characteristics, Randomized Sample

	Placebo N=44	Aripiprazole N=41	Total N=85
AGE (YEARS) (a)			
n	44	41	85
MEAN	10.8	10.1	10.4
MEDIAN	11.0	10.0	10.0
MIN-MAX	6-17	6-16	6-17
S.D.	2.77	2.80	2.79
AGE GROUP, N (%)			
<= 12 YEARS	33 (75.0)	32 (78.0)	65 (76.5)
> 12 YEARS	11 (25.0)	9 (22.0)	20 (23.5)
GENDER, N (%)			
MALE	38 (86.4)	30 (73.2)	68 (80.0)
FEMALE	6 (13.6)	11 (26.8)	17 (20.0)
RACE, N (%)			
WHITE	28 (63.6)	31 (75.6)	59 (69.4)
BLACK/AFRICAN AMERICAN	11 (25.0)	8 (19.5)	19 (22.4)
ASIAN	3 (6.8)	0	3 (3.5)
AMERICAN INDIAN/ALASKA NATIVE	1 (2.3)	0	1 (1.2)
OTHER	1 (2.3)	2 (4.9)	3 (3.5)
ETHNICITY, N (%)			
HISPANIC OR LATINO	9 (20.5)	10 (24.4)	19 (22.4)
NOT HISPANIC OR LATINO	34 (77.3)	29 (70.7)	63 (74.1)

Source: Table 4.3.1 of the CN138603 final CSR
(a) Age assessed at date of first dose of single-blind study medication.
(b) Weight, Height, and BMI assessed at last measurement on or before first day of double-blind dosing in Phase 2.

Table 4.3-1: Demographic Characteristics, Randomized Sample

	Placebo N=44	Aripiprazole N=41	Total N=85
WEIGHT (KG) (b)			
n	44	41	85
MEAN	50.6	51.7	51.1
MEDIAN	44.2	43.6	43.6
MIN-MAX	19-110	21-117	19-117
S.D.	21.91	24.38	23.00
WEIGHT GROUP, N (%)			
< 40 KG	15 (34.1)	17 (41.5)	32 (37.6)
>= 40 KG	29 (65.9)	24 (58.5)	53 (62.4)
HEIGHT (CM) (b)			
n	44	41	85
MEAN	148.6	143.6	146.2
MEDIAN	146.4	142.5	145.0
MIN-MAX	115-186	112-172	112-186
S.D.	18.24	14.24	16.53
BMI (KG/M**2) (b)			
n	44	41	85
MEAN	21.9	24.0	22.9
MEDIAN	20.7	22.6	21.3
MIN-MAX	14-38	15-43	14-43
S.D.	5.19	7.37	6.38

Source: Table 4.3.1 of the CN138603 final CSR
(a) Age assessed at date of first dose of single-blind study medication.
(b) Weight, Height, and BMI assessed at last measurement on or before first day of double-blind dosing in Phase 2.

Table 4.3-2: Baseline Disease Characteristics, Randomized Sample

Variable	Placebo N=44	Aripiprazole N=41	Total N=85
ABC (IRRITABILITY)			
n	44	41	85
MEAN	8.2	9.5	8.8
MEDIAN	8.0	9.0	9.0
MIN-MAX	0-22	0-22	0-22
S.D.	6.20	5.75	5.98
ABC (HYPERACTIVITY)			
n	44	41	85
MEAN	10.1	10.9	10.5
MEDIAN	8.0	10.0	9.0
MIN-MAX	0-36	0-25	0-36
S.D.	9.36	7.16	8.33
ABC (STEREOTYPY)			
n	44	41	85
MEAN	3.9	4.3	4.1
MEDIAN	3.0	5.0	4.0
MIN-MAX	0-13	0-11	0-13
S.D.	3.74	3.42	3.57

Source: Table 4.3.2 of the CN138603 final CSR
Note: Baseline scores assessed at last measurement on or before first day of double-blind dosing in Phase 2.

Table 4.3-2: Baseline Disease Characteristics. Randomized Sample

Variable	Placebo N=44	Aripiprazole N=41	Total N=85
ABC (SOCIAL WITHDRAWAL)			
n	44	41	85
MEAN	5.8	7.5	6.6
MEDIAN	3.0	7.0	5.0
MIN-MAX	0-25	0-20	0-25
S.D.	6.60	6.03	6.35
ABC (INAPPROPRIATE SPEECH)			
n	44	41	85
MEAN	2.1	2.7	2.4
MEDIAN	1.0	2.0	1.0
MIN-MAX	0-9	0-12	0-12
S.D.	2.48	2.96	2.72
CGI-SEVERITY			
n	44	41	85
MEAN	2.9	3.0	3.0
MEDIAN	3.0	3.0	3.0
MIN-MAX	1-6	1-5	1-6
S.D.	1.13	0.89	1.02

Source: Table 4.3.2 of the CN138603 final CSR
Note: Baseline scores assessed at last measurement on or before first day of double-blind dosing in Phase 2.8

Exposure

The number of subjects in the Phase 2 Safety Sample receiving double-blind study medication and the mean and range of the weekly mean daily dose is summarized in Table 4.4. For aripiprazole-treated subjects, the mean weekly daily dose ranged from 8.9 to 10.5 mg/day. The mean daily dose of aripiprazole ranged from 2.0 to 15.0 mg/day.

The mean and range of the weekly mean daily dose of aripiprazole for the Phase 1 Safety Sample are summarized in Table S.4.2 of the CN138603 final CSR1. The mean daily dose of aripiprazole ranged from 2.1 to 12.5 mg/day.

Table 4.4: **Number of Patients Receiving Double-blind Study Medication and Mean and Range of Weekly Mean Daily Dose, Phase 2 Safety Sample**

	Placebo		Aripiprazole			
Days	N	%	N	%	Mean (mg/day)	Min - Max (mg/day)
1-7	43	(100.0)	39	(100.0)	9.2	2.0 - 15.0
8-14	42	(97.7)	39	(100.0)	9.1	2.0 - 15.0
15-21	41	(95.3)	38	(97.4)	9.6	2.0 - 15.0
22-28	39	(90.7)	38	(97.4)	9.6	2.0 - 15.0
29-35	34	(79.1)	33	(84.6)	9.5	2.0 - 15.0
36-42	33	(76.7)	31	(79.5)	9.6	2.0 - 15.0
43-49	29	(67.4)	28	(71.8)	9.2	2.0 - 15.0
50-56	25	(58.1)	28	(71.8)	9.0	2.0 - 15.0
57-63	23	(53.5)	26	(66.7)	8.9	2.0 - 15.0
64-70	22	(51.2)	26	(66.7)	9.1	2.0 - 15.0
71-77	20	(46.5)	26	(66.7)	9.0	2.0 - 15.0
78-84	20	(46.5)	24	(61.5)	8.9	2.0 - 15.0
85-91	19	(44.2)	24	(61.5)	9.2	2.0 - 15.0
92-98	19	(44.2)	23	(59.0)	9.4	2.0 - 15.0
99-105	19	(44.2)	22	(56.4)	9.5	2.0 - 15.0
106-112	19	(44.2)	22	(56.4)	9.6	2.0 - 15.0
> 112	10	(23.3)	11	(28.2)	10.5	5.0 - 15.0

Source: Table 5.1 of the CN138603 final CSR

Efficacy Results

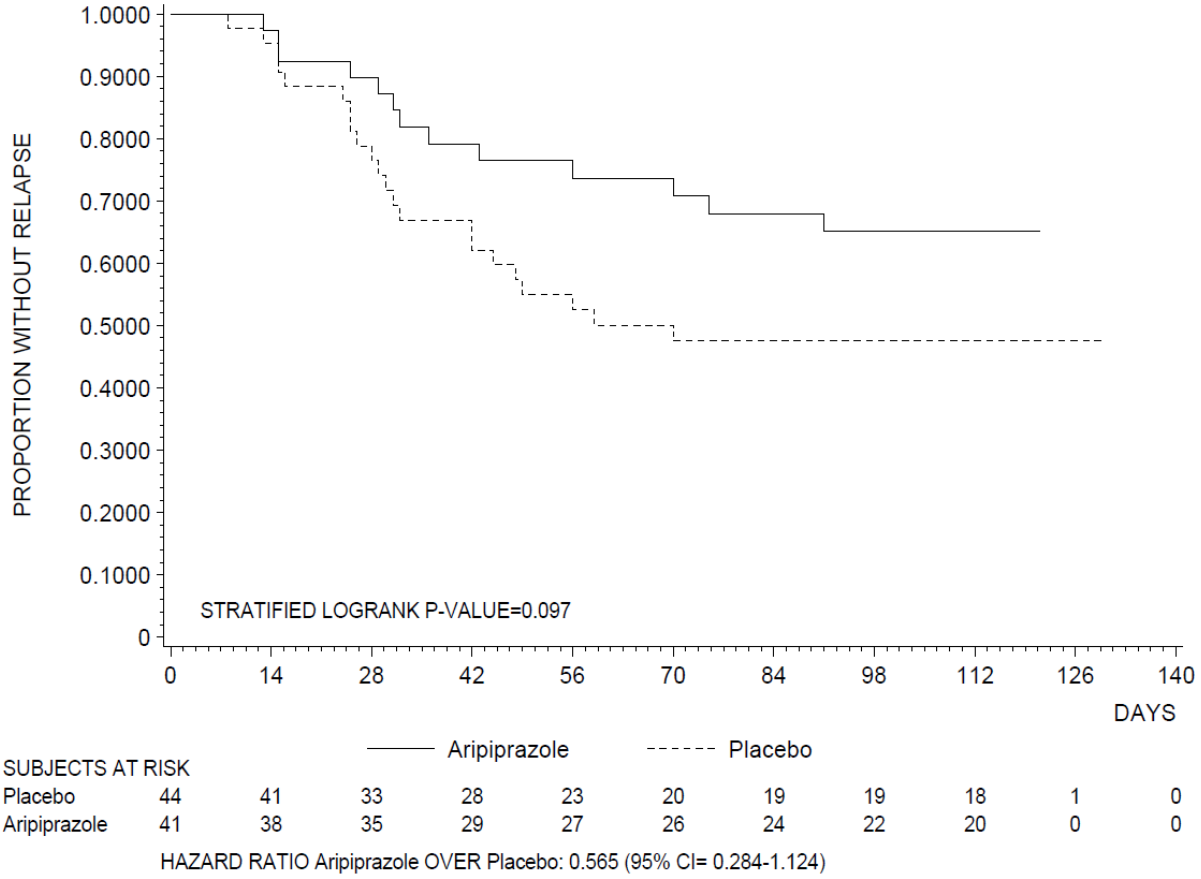
There was no statistically significant difference (p = 0.097) between aripiprazole and placebo for the primary endpoint (time from randomization to relapse) (Randomized Sample). The Kaplan-Meier relapse rates at Week 16 were 32% for aripiprazole and 50% for placebo (hazard ratio of 0.57; 95% CI: 0.28, 1.12).

The mean change from baseline in ABC-I Subscale Score at Week 16 (LOCF data set, Phase 2 Efficacy Sample) was 5.2 and 9.6 in the aripiprazole and placebo groups, respectively (treatment difference of -4.4; 95% CI: -8.8, 0.0). The mean change from baseline in ABC-I Subscale Score at Week 16 (OC data set, Phase 2 efficacy sample) was improved in the aripiprazole group (-1.0) compared with the placebo group (3.6) (treatment difference of -4.55; 95% CI: -8.62, -0.48). The mean endpoint, CGI-I Score at Week 16 (LOCF data set, Phase 2 Efficacy Sample), was 4.2 and 4.8 in the aripiprazole and placebo groups, respectively (treatment difference of -0.6; 95% CI: -1.3, 0.1).

Primary Efficacy Endpoint

There was no statistically significant difference (p = 0.097) between aripiprazole and placebo for the primary endpoint (time from randomization to relapse) (randomized sample) (Figure 4.5 below and Figure S.5.1 and Table S.5.1 of the CN138603 final CSR). The Kaplan-Meier relapse rates at Week 16 were 32% for aripiprazole and 50% for placebo (hazard ratio of 0.57; 95% CI: 0.28, 1.12).

Figure 4.5: Time from Randomization to Relapse, Randomized Sample



Source: Figure 6.1 of the CN138603 final CSR[1]

Secondary Efficacy Endpoints

ABC Irritability (ABC-I) Subscale Scores

The mean change from baseline in ABC-I Subscale Score at Week 16 (LOCF data set, Phase 2 Efficacy Sample) was 5.2 and 9.6 in the aripiprazole and placebo groups, respectively (treatment difference of -4.4; 95% CI: -8.8, 0.0). The mean change from baseline in ABC-I Subscale Score at Week 16 (OC data set, Phase 2 Efficacy Sample) was improved in the aripiprazole group (-1.0) compared with the placebo group (3.6) (treatment difference of -4.55; 95% CI: -8.62, -0.48). The median change from baseline in ABC-I Subscale Score at Week 16 (LOCF data set, Phase 2 Efficacy Sample) was improved in the aripiprazole group (2.0) compared with the placebo group (10.0) (95% CI: 0.0, 10.0). At Phase 1 endpoint, the unadjusted mean change from baseline in ABC-I Subscale Score (OC data set, Phase 1 Efficacy Sample) was improved (-15.5).

Clinical Global Impressions-Improvement (CGI-I) Score

The mean endpoint, CGI-I Score at Week 16 (LOCF data set, Phase 2 Efficacy Sample), was 4.2 and 4.8 in the aripiprazole and placebo groups, respectively (treatment difference of -0.6; 95% CI: -1.3, 0.1). At the Phase 1 endpoint, the unadjusted mean CGI-I Score (LOCF data set, Phase 1 Efficacy Sample) was 2.1.

Additional Efficacy Endpoints

Time from Randomization to Relapse by Subgroups: The Cox proportional hazards model relapse rates at Week 16 for subjects ≤ 12 years were 37.5% and 48.5% for aripiprazole and placebo, respectively (hazard ratio of 0.68; 95% CI: 0.32, 1.43) (Table S.5.6 of the CN138603 final CSR1). The Cox proportional

hazards model relapse rates at Week 16 for subjects > 12 years were 11.1% (1 subject) and 54.5% for aripiprazole and placebo, respectively (hazard ratio of 0.18; 95% CI: 0.02, 1.51).

SAFETY

No deaths were reported in this study.

Phase 2 Safety Sample

No subjects had serious adverse events (SAEs). One subject had an adverse event (AE) that started in Phase 1 and was randomized in error in Phase 2; this subject did not receive treatment in Phase 2. No treated subjects discontinued due to AEs.

The overall incidence of treatment-emergent AEs was higher in the aripiprazole group (56.4%) than in the placebo group (32.6%).

Treatment-emergent AEs in ≥ 5% of subjects in either the aripiprazole or placebo groups were upper respiratory tract infection (10.3% vs 2.3%), constipation and movement disorder (5.1% each vs 0% each), and vomiting (5.1% vs 4.7%).

Three subjects (7.7%) in the aripiprazole group had treatment-emergent extrapyramidal symptom (EPS)-related AEs (movement disorder in 2 subjects and akathisia, extrapyramidal disorder, and tremor in 1 subject each). In the placebo group, 3 subjects (7.0%) had treatment-emergent EPS-related AEs (akathisia, muscle twitching, and tremor in 1 subject each).

The median changes from baseline in laboratory values to endpoint were generally similar between the aripiprazole and placebo groups; however, numerical differences were observed for relative eosinophils, creatine kinase, prolactin, and uric acid. Few clinically relevant laboratory abnormalities were observed, except for non-fasting triglycerides and combined triglycerides: there were potentially significant changes in 6/20 in placebo (withdrawal) and 10/17 in aripiprazole group.

Table S.7.1

Protocol: CN138603 Page 2 of 2

Number of Patients with Potentially Clinically Relevant Laboratory Abnormalities During Phase 2, Phase 2 Safety Sample

LAB MEASUREMENT	Incidence (%) Placebo	Aripiprazole
Cholesterol, HDL Fasting (mg/dL)	0/ 18 (0.0)	0/ 19 (0.0)
Cholesterol, HDL Non-Fasting (mg/dL)	1/ 20 (5.0)	1/ 17 (5.9)
Cholesterol, LDL Combined (mg/dL)	0/ 38 (0.0)	1/ 34 (2.9)
Cholesterol, LDL Fasting (mg/dL)	0/ 18 (0.0)	1/ 19 (5.3)
Cholesterol, LDL Non-Fasting (mg/dL)	0/ 20 (0.0)	0/ 17 (0.0)
Cholesterol, Total Combined (mg/dL)	0/ 38 (0.0)	1/ 34 (2.9)
Cholesterol, Total Fasting (mg/dL)	0/ 18 (0.0)	1/ 19 (5.3)
Cholesterol, Total Non-Fasting (mg/dL)	0/ 20 (0.0)	0/ 17 (0.0)
Glucose, Combined (mg/dL)	0/ 38 (0.0)	1/ 34 (2.9)
Glucose, Fasting Serum (mg/dL)	0/ 18 (0.0)	1/ 19 (5.3)
Glucose, Non-Fasting Serum (mg/dL)	0/ 20 (0.0)	0/ 17 (0.0)
Triglycerides, Combined (mg/dL)	7/ 38 (18.4)	13/ 34 (38.2)
Triglycerides, Fasting (mg/dL)	1/ 18 (5.6)	3/ 19 (15.8)
Triglycerides, Non-Fasting (mg/dL)	6/ 20 (30.0)	10/ 17 (58.8)

Median change for non fasting triglycerides values were -7.0 mg/dL in the placebo (withdrawal group) vs 2.0 mg/dL in the aripiprazole group. Median change for combined triglycerides values were 7.0 mg/dL in the placebo (withdrawal group) vs 10.0 mg/dL in the aripiprazole

group.

Table S.7.5

Protocol: CN138603 Page 9 of 9

Median Change from Baseline in Laboratory Measurements During Phase 2, Phase 2 Safety Sample

	Median Change from Baseline (Median Actual Score for Baseline)				Treatment Comparison P-values (a)
	Placebo		Aripiprazole		Ari./Plac.
Visit	N	Median	N	Median	
Triglycerides, Combined (mg/dL)					
Baseline	35	92.0	32	99.0	0.292
Endpoint	35	7.0	32	10.0	0.905
Highest Value	35	7.0	32	12.0	0.711
Triglycerides, Fasting (mg/dL)					
Baseline	15	73.0	15	100.0	0.044
Endpoint	15	3.0	15	-2.0	0.950
Highest Value	15	3.0	15	-2.0	0.950
Triglycerides, Non-Fasting (mg/dL)					
Baseline	11	127.0	8	122.0	0.563
Endpoint	11	-7.0	8	2.0	0.591
Highest Value	11	-7.0	8	2.0	0.591
Uric Acid (mg/dL)					
Baseline	35	4.3	32	4.6	0.425
Endpoint	35	0.1	32	0.5	0.024
Highest Value	35	0.1	32	0.5	0.023

(a) Wilcoxon rank-sum test is used for all comparisons.

The adjusted mean change from baseline in serum prolactin (OC data set and Week 16 LOCF) was -0.2 and 4.6 ng/mL in the aripiprazole and placebo groups, respectively.

The median changes from baseline in vital signs to endpoint were similar in both treatment groups. Few potentially clinically relevant vital sign abnormalities were observed, except for a decrease in supine diastolic blood pressure (DBP) and a decrease in standing DBP. The adjusted mean change from baseline to Week 16 (LOCF) in weight was significantly greater in the aripiprazole group (2.2 kg) than in the placebo group (0.6 kg). Only 2 subjects (both in the placebo group) had relevant weight loss.

Phase 1 Safety Sample

One subject had an SAE (aggression) that was not considered related to aripiprazole by the investigator. Thirteen subjects (8.4%) had AEs that led to discontinuation; the only AEs that led to discontinuation reported in > 1 subject were aggression and weight increased (1.3% each). Eighty percent of subjects had treatment-emergent AEs, and the most common events were weight increased, somnolence, and vomiting. Twenty-seven subjects (17.4%) had treatment-emergent EPS-related AEs, and the only treatment-emergent EPS-related AE reported in ≥ 5% of subjects was tremor (6.5%).

Few clinically relevant laboratory abnormalities were observed, except for non-fasting triglycerides and combined triglycerides, which have changed from a) nonfasting: a median 101 at baseline to 112 at

endpoint, and b) combined median 88 at baseline to 92 at endpoint:

Table S.7.6

Protocol: CN138603 Page 6 of 6

Median Change from Baseline in Laboratory Measurements During Phase 1,
Phase 1 Safety Sample

	Median Change from Baseline (Median Actual Score for Baseline)	
	Overall	
Visit	N	Median
Prolactin (ng/mL)		
Baseline	107	5.0
Endpoint	107	-3.0
Sodium, Serum (mEq/L)		
Baseline	110	140.0
Endpoint	110	0.0
Triglycerides, Combined (mg/dL)		
Baseline	110	88.0
Endpoint	110	3.0
Triglycerides, Fasting (mg/dL)		
Baseline	41	81.0
Endpoint	41	4.0
Triglycerides, Non-Fasting (mg/dL)		
Baseline	31	101.0
Endpoint	31	11.0
Uric Acid (mg/dL)		
Baseline	110	4.2
Endpoint	110	0.1

Program Source: S:\RHO\BMS\Abilify\Studies\CN138603\Tables\rt-lb-medlabsaf1.sas 17AUG2012:11:51:47

Table S.7.2

Protocol: CN138603 Page 2 of 2

Number of Patients with Potentially Clinically Relevant Laboratory Abnormalities During Phase 1,
Phase 1 Safety Sample

LAB MEASUREMENT	Incidence (%) Overall
Cholesterol, HDL Non-Fasting (mg/dL)	3/ 62 (4.8)
Cholesterol, LDL Combined (mg/dL)	1/116 (0.9)
Cholesterol, LDL Fasting (mg/dL)	0/ 55 (0.0)
Cholesterol, LDL Non-Fasting (mg/dL)	1/ 61 (1.6)
Cholesterol, Total Combined (mg/dL)	0/117 (0.0)
Cholesterol, Total Fasting (mg/dL)	0/ 55 (0.0)
Cholesterol, Total Non-Fasting (mg/dL)	0/ 62 (0.0)
Glucose, Combined (mg/dL)	2/117 (1.7)
Glucose, Fasting Serum (mg/dL)	2/ 55 (3.6)
Glucose, Non-Fasting Serum (mg/dL)	0/ 63 (0.0)
Triglycerides, Combined (mg/dL)	27/117 (23.1)
Triglycerides, Fasting (mg/dL)	6/ 55 (10.9)
Triglycerides, Non-Fasting (mg/dL)	20/ 62 (32.3)

Program Source: S:\RHO\BMS\Abilify\Studies\CN138603\Tables\rt-lb-abnumsaf1.sas 07AUG2012:15:12:13

The unadjusted mean change from baseline in serum prolactin at endpoint was -4.7 ng/mL. Potentially clinically relevant vital sign abnormalities observed in ≥ 10% of subjects were a decrease in sitting DBP, sitting systolic blood pressure (SBP), standing SBP and DBP, and supine SBP and DBP and an increase in

sitting DBP. Mean and median changes from baseline to Week 26 in weight generally increased over time. Eleven subjects had potentially clinically relevant electrocardiogram (ECG) abnormalities (sinus tachycardia in 3 subjects, ventricle premature beat in 1 subject, and other abnormalities in 7 subjects).

Other Serious Adverse Events

No subjects in the Phase 2 Safety Sample had SAEs.

In the Phase 1 Safety Sample, 1 subject (CN138603-37-47) had Grade 3 aggression that was not considered related to aripiprazole by the investigator. Aripiprazole was discontinued, and the event resolved with sequela.

One enrolled subject (CN138603-1-2) had SAEs that started before or during the screening phase of the study (Grade 3 worsening of aggression and Grade 3 delusions) that were not considered related to the study drug by the investigator; the events resolved without treatment.

Adverse Events Leading to Discontinuation of Study Therapy

One subject had an AE that started in Phase 1 and was randomized in error in Phase 2; this subject did not receive treatment in Phase 2. None of the treated subjects in the Phase 2 Safety Sample discontinued due to AEs. In the Phase 1 Safety Sample, 13 subjects (8.4%) had AEs that led to discontinuation. Adverse events that led to discontinuation reported in > 1 subject were aggression and weight increased (2 subjects [1.3%] each). No subjects discontinued due to AEs with onset before or during the screening phase.

Overall Adverse Events

In the Phase 2 Safety Sample, the overall incidence of treatment-emergent AEs was higher in the aripiprazole group (56.4%) than in the placebo group (32.6%). Treatment-emergent AEs in ≥ 5% of subjects in either the aripiprazole or placebo groups were upper respiratory tract infection (10.3% vs 2.3%), constipation and movement disorder (5.1% each vs 0% each), and vomiting (5.1% vs 4.7%).

In the Phase 1 Safety Sample, 80.0% of subjects had treatment-emergent AEs. Treatment-emergent AEs reported in ≥ 5% of subjects were weight increased (25.2%), somnolence (14.8%), vomiting (14.2%), increased appetite (12.9%), upper respiratory tract infection (10.3%), fatigue and insomnia (8.4% each), diarrhea (7.1%), tremor (6.5%), aggression and nasopharyngitis (5.8% each), headache, lethargy, and pyrexia (5.2% each).

Treatment-related Adverse Events

In the Phase 2 Safety Sample, the overall incidence of treatment-related AEs was higher in the aripiprazole group (23.1%) than in the placebo group (14.0%). All treatment-related AEs were reported in < 5% of subjects in either treatment group (Table below).

In the Phase 1 Safety Sample, 59.4% of subjects had treatment-related AEs. Treatment-related AEs reported in ≥ 5% of subjects were weight increased (23.9%), increased appetite and somnolence (12.9% each), fatigue (7.7%), tremor (6.5%), and insomnia (5.8%).

Table 5.3.1: Incidence of Treatment-related Adverse Events During Phase 2, Phase 2 Safety Sample

SYSTEM ORGAN CLASS PREFERRED TERM	Incidence (%) Placebo N = 43	 Aripiprazole N = 39
NUMBER OF PATIENTS SCREENED FOR AES	43	39
NUMBER OF MALE PATIENTS	37	28
NUMBER OF FEMALE PATIENTS	6	11
ANY TREATMENT-RELATED ADVERSE EVENT	6 (14.0)	9 (23.1)
GASTROINTESTINAL DISORDERS	1 (2.3)	3 (7.7)
CONSTIPATION	0	1 (2.6)
SALIVARY HYPERSECRETION	0	1 (2.6)
VOMITING	1 (2.3)	1 (2.6)
NERVOUS SYSTEM DISORDERS	2 (4.7)	3 (7.7)
AKATHISIA	1 (2.3)	1 (2.6)
EXTRAPYRAMIDAL DISORDER	0	1 (2.6)
GLABELLAR REFLEX ABNORMAL	0	1 (2.6)
MOVEMENT DISORDER	0	1 (2.6)
TREMOR	1 (2.3)	1 (2.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (2.6)
THROMBOCYTOSIS	0	1 (2.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (2.3)	1 (2.6)
FATIGUE	0	1 (2.6)
IRRITABILITY	1 (2.3)	0

Source: Table 7.6.1 of the CN138603 final CSR
(M)/(F): Incidence of AEs adjusted for Males/Females
MedDRA version 15 coding dictionary.

Table 5.3.1: Incidence of Treatment-related Adverse Events During Phase 2, Phase 2 Safety Sample

SYSTEM ORGAN CLASS PREFERRED TERM	Incidence (%) Placebo N = 43	 Aripiprazole N = 39
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (2.6)
EXCORIATION	0	1 (2.6)
METABOLISM AND NUTRITION DISORDERS	2 (4.7)	1 (2.6)
INCREASED APPETITE	2 (4.7)	1 (2.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (2.3)	1 (2.6)
JOINT RANGE OF MOTION DECREASED	0	1 (2.6)
MUSCLE TWITCHING	1 (2.3)	0
PSYCHIATRIC DISORDERS	1 (2.3)	1 (2.6)
INSOMNIA	0	1 (2.6)
RESTLESSNESS	1 (2.3)	0

Source: Table 7.6.1 of the CN138603 final CSR

(M)/(F): Incidence of AEs adjusted for Males/Females
MedDRA version 15 coding dictionary.

Treatment-emergent Adverse Events by Intensity

In the Phase 2 Safety Sample, the majority of treatment-emergent AEs were mild in intensity. No Grade 4 treatment-emergent AEs were reported. Two subjects had Grade 3 treatment-emergent AEs (sinusitis in 1 subject in the aripiprazole group and aggression and irritability in 1 subject in the placebo group). In the Phase 1 Safety Sample, the majority of treatment-emergent AEs were mild in intensity. No Grade 4 treatment-emergent AEs were reported. Six subjects had Grade 3 treatment-emergent AEs (weight increased in 4 subjects and aggression in 2 subjects).

Treatment-emergent Adverse Events During Phase 2 by Subgroup

By Gender

In the Phase 2 Safety Sample, the overall incidence of treatment-emergent AEs was lower in male subjects in the aripiprazole group (42.9%) than in female subjects (90.9%). In the placebo group, the overall incidence of treatment-emergent AEs was similar in male and female (32.4% and 33.3%, respectively).

By Age

In the Phase 2 Safety Sample, the overall incidence of treatment-emergent AEs was greater in subjects > 12 years in the aripiprazole group (62.5%) than in subjects „T 12 years (54.8%). In the placebo group, the overall incidence of treatment-emergent AEs was also greater in subjects > 12 years (36.4%) than in subjects ≤ 12 years (31.3%).

By Race

In the Phase 2 Safety Sample, the overall incidence of treatment-emergent AEs was greater in White subjects in the aripiprazole group (62.1%) than in non-White subjects (40.0%). In the placebo group, the overall incidence of treatment-emergent AEs was also greater in White subjects (35.7%) than in non-White subjects (26.7%).

Clinical Laboratory Evaluations

In the Phase 2 Safety Sample, the median changes from baseline in laboratory values to endpoint were generally similar between the aripiprazole and placebo groups; however, differences were observed for relative eosinophils, creatine kinase, prolactin, and uric acid. Few clinically relevant laboratory abnormalities were observed, except for non-fasting triglycerides and combined triglycerides. In the Phase 2 Safety Sample, the adjusted mean change from baseline in serum prolactin (OC data set and Week 16 LOCF) was -0.2 and 4.6 ng/mL in the aripiprazole and placebo groups, respectively (treatment difference of -4.81; CI: -6.77, -2.85).

In the Phase 1 Safety Sample, the median changes from baseline in laboratory values to endpoint are summarized in Table S.7.6. Few clinically relevant laboratory abnormalities were observed, except for non-fasting triglycerides (32.3%) and combined triglycerides (23.1%).

In the Phase 1 Safety Sample, the unadjusted mean change from baseline in serum prolactin at endpoint was -4.7 ng/mL.

Electrocardiograms

In the Phase 1 Safety Sample, the mean change from baseline in ECG parameters is summarized in Table S.7.11 of the CN138603 final CSR1:

Table S.7.11

Protocol: CN138603 Page 1 of 1

Median Change from Baseline in ECG Measurements During Phase 1,
Phase 1 Safety Sample

	Median Change from Baseline (Median Actual Score for Baseline)	
	Overall	
Visit	N	Median
QTc Bazett (msec)		
Baseline	117	415.0
Endpoint	117	2.0
QTc Friderica (msec)		
Baseline	117	390.0
Endpoint	117	0.0
PR (msec)		
Baseline	117	134.0
Endpoint	117	4.0
RR (msec)		
Baseline	117	708.0
Endpoint	117	-20.0
QRS (msec)		
Baseline	117	80.0
Endpoint	117	0.0
Heart Rate (bpm)		
Baseline	117	84.0
Endpoint	117	2.0

Eleven subjects had ECG abnormalities (sinus tachycardia in 3 subjects, ventricle premature beat in 1 subject, and other abnormalities in 7 subjects):

Table S.7.9

Protocol: CN138603 Page 1 of 1

Number of Patients with Potentially Clinically Relevant ECG Abnormalities During Phase 1,
Phase 1 Safety Sample

ECG ABNORMALITY	Incidence (%) Overall
NUMBER OF PATIENTS IN SAFETY SAMPLE	155
Sinus tachycardia	3/126 (2.4)
Sinus bradycardia	0/126 (0.0)
Supravent. premature beat	0/126 (0.0)
Vent. premature beat	1/126 (0.8)
Supravent. tachycardia	0/126 (0.0)
Vent. tachycardia	0/126 (0.0)
Atrial fibrillation	0/126 (0.0)
Atrial flutter	0/126 (0.0)
1st deg A-V block	0/126 (0.0)
2nd deg A-V block	0/126 (0.0)
3rd deg A-V block	0/126 (0.0)
LBB block	0/126 (0.0)
RBB block	0/126 (0.0)
Pre-excitation syndrome	0/126 (0.0)
Other intravent. block	0/126 (0.0)
Acute infarction	0/126 (0.0)
Subacute (recent) infarction	0/126 (0.0)
Old infarction	0/126 (0.0)
Myocardial ischemia	0/126 (0.0)
Symmetrical T-wave inversion	0/126 (0.0)
QTcB interval (msec)	0/126 (0.0)
QTcF interval (msec)	0/126 (0.0)
Other Abnormality	7/126 (5.6)

Table S.7.10

Protocol: CN138603 Page 1 of 1

Patients with Potentially Clinically Relevant ECG Abnormalities During Phase 1, Phase 1 Safety Sample

Patient ID	Measurement	Baseline Value	Abnormal Value	Study Day #
CN138603-2-73	Sinus tachycardia	85	202	95
CN138603-15-121	Other abnormality	0	1	127
CN138603-16-183	Sinus tachycardia	125	152	50
CN138603-21-16	Sinus tachycardia	104	142	122
CN138603-21-18	Other abnormality	0	1	101
CN138603-21-101	Other abnormality	0	1	158
CN138603-21-103	Other abnormality	0	1	92
CN138603-43-13	Other abnormality	0	1	103
CN138603-43-70	Other abnormality	0	1	112
CN138603-51-66	Vent. Premature beat	0	1	159
CN138603-51-145	Other abnormality	0	1	128

Note: BASELINE/ABNORMAL VALUE for Qualitative ECG data: 0 = not present, 1 = present
+ Abnormality occurred more than 30 days after last single-blind aripiprazole dosing date.
# Based on first day of single-blind aripiprazole treatment.

Program Source: S:\RHO\BMS\Abilify\Studies\CN138603\Listings\rl-eg-aballsaf1.sas 07AUG2012:14:25:10

"Other abnormalities" meant single visit abnormalities as stated: pt 15-121: prolonged QTcB: 439 msec; pt 21-18: prolonged QTcB 448; pt 21-10: QTcF increased >10% (from 370 to 409); pt 21-103: prolonged QTcB: 439; pt 43-13: prolonged QTcB: 436; pt 43-70: prolonged QTcB: 445; pt 51-145: prolonged QTcB: 438 and 1st AV block (PR 170 msec).

Vital Signs and Physical Findings

Vital Signs

In the Phase 2 Safety Sample, the median changes from baseline in vital signs to endpoint were similar in both treatment groups. Few potentially clinically relevant vital sign abnormalities were observed, except for a decrease in supine DBP (15.6% and 16.7% in the aripiprazole and placebo groups, respectively) and a decrease in standing DBP (13.5% and 12.2% in the aripiprazole and placebo groups, respectively). In the Phase 1 Safety Sample, the median changes from baseline in vital signs to Week 26 are summarized in Table S.7.17 of the CN138603 final CSR1. Potentially clinically relevant vital sign abnormalities observed in ≥10% of subjects were a decrease in sitting DBP (53.5%), a decrease in sitting SBP (46.5%), a decrease in standing SBP and DBP (20.4% each), a decrease in supine SBP and DBP (17.4% each), and an increase in sitting DBP (11.6%).

Physical Examination Findings

In the Phase 2 Safety Sample, no differences in height were observed between the aripiprazole and placebo groups. The change from baseline in body mass index (BMI) at Week 16 was significantly greater in the aripiprazole group than in the placebo group across all analyses, except for the median percentile change in BMI.

In the Phase 1 Safety Sample, mean and median changes from baseline to Week 26 in height varied slightly over time. An may reflect the challenges of securing subject cooperation with a height measurement in this patient population. Mean and median changes from baseline to Week 26 in BMI varied slightly over time.

Tanner Staging

In the Phase 2 Safety Sample, the number of subjects who advanced a Tanner stage for pubic hair was 3 and 4 in the aripiprazole and placebo groups, respectively. The number of subjects who advanced a Tanner stage for breast/genitals was 5 and 4 in the aripiprazole and placebo groups, respectively. In the Phase 1

Safety Sample, 24 and 21 subjects advanced a Tanner stage for pubic hair and breast/genitals, respectively.

Other Observations Related to Safety

Weight Increase or Loss

In the Phase 2 Safety Sample, the adjusted mean change from baseline to Week 16 (LOCF) in weight z-score was significantly greater in the aripiprazole group (0.1 kg) than in the placebo group (-0.0 kg) (treatment difference of 0.15; 95% CI: 0.06, 0.24):

Adjusted Mean Change from Baseline in Weight (kg) Z-score, OC Data Set and Week 16 LOCF, Phase 2 Safety Sample

	Adjusted Mean Change from Baseline (Mean Actual Score for Baseline) (a)					
	Placebo			Aripiprazole		
Visit	N	Mean	SE	N	Mean	SE
Baseline	43	0.8	0.20	39	1.3	0.21
Week 2	36	-0.0	0.02	36	0.1	0.02
Week 4	36	-0.0	0.02	33	0.0	0.02
Week 6	33	-0.0	0.03	29	0.0	0.03
Week 8	25	0.1	0.12	27	0.1	0.11
Week 10	19	-0.0	0.05	25	0.1	0.04
Week 12	19	-0.0	0.06	23	0.1	0.05
Week 14	19	-0.0	0.06	23	0.1	0.05
Week 16	19	-0.1	0.06	20	0.2	0.05
Week 16 (LOCF)	43	-0.0	0.03	39	0.1	0.03
Highest Value	43	0.1	0.07	39	0.2	0.08
Week 16 (LOCF)						
Treatment Difference, 95% CI:					0.15 (0.06,0.24)	
p-value:					0.001	
Highest Value						
Treatment Difference, 95% CI:					0.07 (-0.14,0.28)	
p-value:					0.488	

(a) ANOVA model, controlling for treatment, is used for baseline. ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline. Means, differences in means, 95% CI for the differences and p-values are based on the ANOVA/ANCOVA model.

Program Source: S:\RHO\BMS\Abilify\Studies\CN138603\Tables\rt-vs-wtzocsaf2.sas 07AUG2012:14:13:37

Phase 1 Safety Sample mean and median changes from baseline to Week 26 in weight are summarized below:

Unadjusted Mean and Median Change from Baseline in Weight (kg), Phase 1 Endpoint, Phase 1 Safety Sample

	Mean and Median Change from Baseline (Mean and Median Actual Score for Baseline) (a) Overall			
Visit	N	Mean	Median	SE
Baseline	152	46.2	39.6	1.84
Week 1	144	-0.0	0.0	0.08
Week 2	147	-0.0	0.0	0.09
Week 4	147	0.8	0.5	0.27
Week 6	141	1.1	0.9	0.14
Week 10	124	2.2	1.9	0.20
Week 14	115	3.0	2.7	0.29
Week 18	71	3.7	3.1	0.40
Week 22	26	3.5	2.9	0.60
Week 26	7	2.6	2.5	1.01
Week 26 (LOCF)	152	3.2	2.8	0.28

(a) Sample means, sample medians, and sample standard errors are presented.

Program Source: S:\RHO\BMS\Abilify\Studies\CN138603\Tables\rt-vs-wtsaf1.sas 16AUG2012:11:33:16

Median Change from Baseline in Weight During Phase 2,
Phase 2 Safety Sample

Visit	Median Change from Baseline (Median Actual Value for Baseline)						Treatment Comparisons P-values (a)
	Placebo			Aripiprazole			
	N	Median	(Q1, Q3)	N	Median	(Q1, Q3)	Ari./Plac.
Weight (kg)							
Baseline	43	43.5	(35.7, 58.2)	39	43.6	(33.6, 69.4)	0.985
Endpoint	43	0.3	(-0.6, 1.5)	39	1.5	(0.6, 3.6)	<0.001
Highest Value	43	0.7	(0.1, 1.8)	39	2.2	(0.8, 4.0)	<0.001

Q1 = lower quartile, Q3 = upper quartile.
(a) Wilcoxon rank-sum test is used for all comparisons.

Program Source: S:\RHO\BMS\Abilify\Studies\CN138603\Tables\rt-vs-medwtsaf2.sas 07AUG2012:14:12:52

Unadjusted Mean and Median Change from Baseline in Weight (kg) Z-score, Phase 1 Endpoint,
Phase 1 Safety Sample

Visit	Mean and Median Change from Baseline (Mean and Median Actual Score for Baseline) (a) Overall			
	N	Mean	Median	SE
Baseline	152	0.9	0.9	0.11
Week 1	144	0.0	0.0	0.01
Week 2	147	-0.0	0.0	0.01
Week 4	147	0.0	0.0	0.02
Week 6	141	0.1	0.0	0.02
Week 10	124	0.1	0.1	0.02
Week 14	115	0.1	0.1	0.05
Week 18	71	0.2	0.1	0.04
Week 22	26	0.2	0.2	0.07
Week 26	7	0.0	0.0	0.12
Week 26 (LOCF)	152	0.2	0.1	0.04

(a) Sample means, sample medians, and sample standard errors are presented.

Program Source: S:\RHO\BMS\Abilify\Studies\CN138603\Tables\rt-vs-wtzsaf1.sas 16AUG2012:11:33:25

Extrapyramidal Symptom (EPS)-related Side Effects

EPS-related side effects of dyskinesias, akathisia, parkinsonism, and other unwanted effects of psychotropics were evaluated with the following standardized and generally recognized scales: Abnormal Involuntary Movement Scale (AIMS),2 Barnes Akathisia Rating Scale (BARS),3 and Simpson Angus Scale (SAS).4

In the Phase 2 Safety Sample, 3 subjects (7.7%) in the aripiprazole group had treatment-emergent EPS-related AEs (movement disorder in 2 subjects and akathisia, extrapyramidal disorder, and tremor in 1 subject each). In the placebo group, 3 subjects (7.0%) had treatment-emergent EPS-related AEs (akathisia, muscle twitching, and tremor in 1 subject each):

Incidence of Treatment-Emergent EPS-Related Adverse Events During Phase 2,
Phase 2 Safety Sample

EPS CATEGORY PREFERRED TERM	Incidence (%) Placebo N = 43	 Aripiprazole N = 39
NUMBER OF PATIENTS SCREENED FOR AES	43	39
NUMBER OF MALE PATIENTS	37	28
NUMBER OF FEMALE PATIENTS	6	11
ANY EPS-RELATED ADVERSE EVENT	3 (7.0)	3 (7.7)
PARKINSONISM EVENTS	1 (2.3)	3 (7.7)
MOVEMENT DISORDER	0	2 (5.1)
EXTRAPYRAMIDAL DISORDER	0	1 (2.6)
TREMOR	1 (2.3)	1 (2.6)
AKATHISIA EVENTS	1 (2.3)	1 (2.6)
AKATHISIA	1 (2.3)	1 (2.6)
RESIDUAL EVENTS	1 (2.3)	0
MUSCLE TWITCHING	1 (2.3)	0

(M)/(F): Incidence of AEs adjusted for Males/Females
MedDRA version 15 coding dictionary.

Program Source: S:\RHO\BMS\Abilify\Studies\CN138603\Tables\rt-ae-teepssaf2.sas 07AUG2012:14:02:29

In the Phase 1 Safety Sample, 27 subjects (17.4%) had treatment-emergent EPS-related AEs. The only treatment-emergent EPS-related AE reported in ≥ 5% of subjects was tremor (6.5%):

Incidence of Treatment-Emergent EPS-Related Adverse Events During Phase 1,
Phase 1 Safety Sample

EPS CATEGORY PREFERRED TERM	Incidence (%) Overall N = 155
NUMBER OF PATIENTS SCREENED FOR AES	155
NUMBER OF MALE PATIENTS	123
NUMBER OF FEMALE PATIENTS	32
ANY EPS-RELATED ADVERSE EVENT	27 (17.4)
PARKINSONISM EVENTS	17 (11.0)
TREMOR	10 (6.5)
EXTRAPYRAMIDAL DISORDER	3 (1.9)
MOVEMENT DISORDER	3 (1.9)
GAIT DISTURBANCE	1 (0.6)
DYSTONIC EVENTS	8 (5.2)
MUSCULOSKELETAL STIFFNESS	6 (3.9)
TIC	2 (1.3)
AKATHISIA EVENTS	7 (4.5)
AKATHISIA	6 (3.9)
PSYCHOMOTOR HYPERACTIVITY	1 (0.6)
DYSKINETIC EVENTS	7 (4.5)
DROOLING	5 (3.2)
TARDIVE DYSKINESIA	2 (1.3)
DYSKINESIA	1 (0.6)

(M)/(F): Incidence of AEs adjusted for Males/Females
MedDRA version 15 coding dictionary.

Program Source: S:\RHO\BMS\Abilify\Studies\CN138603\Tables\rt-ae-teepssaf1.sas 07AUG2012:14:02:23

Abnormal Involuntary Movement Scale (AIMS)

In the Phase 2 Safety Sample, the adjusted mean change from baseline in AIMS Total Score to Week 16 (OC data set and LOCF) was similar in the aripiprazole group (-0.1) and the placebo group (0.1) (treatment difference of -0.15; 95% CI: -0.50, 0.19). In the Phase 1 Safety Sample, the unadjusted mean change from baseline in AIMS Total Score to Week 26 (LOCF) was -0.4.

Simpson Angus Scale (SAS)

In the Phase 2 Safety Sample, the adjusted mean change from baseline in SAS Score to Week 16 (OC data set and LOCF) was significantly greater in the aripiprazole group (-0.3) than in the placebo group (0.0) (treatment difference of -0.37; 95% CI: -0.73, -0.00;). In the Phase 1 Safety Sample, the unadjusted mean change from baseline in SAS Score to Week 26 (LOCF) was -0.4.

Barnes Akathisia Rating Scale (BARS)
In the Phase 2 Safety Sample, the adjusted mean change from baseline in BARS Score to Week 16 (OC data set and LOCF) was similar in the aripiprazole group (-0.1) and the placebo group (0.0) (treatment difference of -0.10; 95% CI: -0.23, -0.03). In the Phase 1 Safety Sample, the unadjusted mean change from baseline in BARS Score to Week 26 (LOCF) was -0.1.

OVERALL CONCLUSIONS
Aripiprazole did not achieve statistical significance vs placebo on the primary outcome measure, the time to relapse. The effect size observed was smaller than what was used to power the study. Similar findings were observed on the 2 secondary outcome measures: mean change from baseline (end of Phase 1) to Week 16 endpoint (LOCF) in ABC-I score, and mean CGI-I score at Week 16 endpoint (LOCF).
No SAEs or discontinuations of treatment due to AEs occurred during the randomized phase. AEs were as expected with aripiprazole in pediatric subjects. The Week 16 LOCF mean change in weight z-score during Phase 2 was -0.0 in the placebo group and 0.1 in the aripiprazole group. During Phase 2, median changes were small in both the aripiprazole and placebo groups on fasting total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, glucose, and triglycerides.

BENEFITS AND RISKS CONCLUSIONS
The results from Study CN138603 do not change the overall benefit/risk profile of aripiprazole.

Assessment
MAH has presented the final results of a randomised withdrawal study to assess safety / maintenance of efficacy beyond 3 months (12 weeks) for paediatric patients with irritability associated with autistic disorder with ages 6 to 17 years old, requested by FDA as a post approval commitment.
Analysis of data do not raise particular concerns in efficacy beyond 12 weeks in the presented indication, although some tolerance seem to develop. Presented efficacy data do not jeopardise any of the EU approved indications.
Regarding safety, there were relevant adverse events occurring in paediatric population, both in frequency and in severity, as compared to the adult population, namely concerning weight gain and EPS.
These however are in line with the adverse event profile observed in the main studies which led to approval of the paediatric indications.
Regarding the cardiac effects and the changes in QTc since there was at least a case with QTc increase above > 30 msec, the MAH should continue monitoring effects on ECG and cardiac AEs and present the data in the PSURs.
The drop out rate due to lack of efficacy and / or adverse events is very high (46%). These values however, are within the range of both aripiprazole in other indications and age ranges and of other antipsychotics in autism. During stabilization phase most patients / caregivers may withdraw their consent without further notice, and lack of efficacy vs intolerance cannot be disentangled. On the other hand, in phase 2, when caregivers know that the pt may be under placebo, drop out due to lack of efficacy is expected. Thus we would also not consider this high drop out rate as unexpected.

The MAH has received the initial proposal of SmPC change where we proposed for Section 5.1:
Where it reads:
"Irritability associated with autistic disorder in paediatric patients (see section 4.2):
Aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour

Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole."

Should read (appended text underlined):

"Irritability associated with autistic disorder in paediatric patients (see section 4.2):

Aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Aripiprazole was also studied in a placebo-controlled withdrawal safety study, after a 13-26 week stabilisation on aripiprazole 2-15 mg; after this period, patients were either maintained on aripiprazole or switched to placebo for further 16 weeks. The objective was to evaluate the efficacy of aripiprazole compared with placebo to prevent relapses in pediatric subjects who maintained a response for 12 weeks of aripiprazole treatment. Relapse rates at Week 16 were 32% for aripiprazole and 50% for placebo (non statistically significant difference).There was an increase in median weight of 2.5 Kg in the stabilisation phase on aripiprazole, and a further median increase on aripiprazole (1.5 Kg) as compared to placebo (0.3 Kg) in the second phase of the study. Extrapyramidal symptoms were also reported in 17% of patients, with tremor totalling 6.5%."

The MAH has proposed the new version:

Aripiprazole was also studied in patients aged 6 to 17 years in a placebo-controlled, long-term maintenance trial. After a 13-26 week stabilisation on aripiprazole (2-15 mg/day) patients with a stable response were either maintained on aripiprazole or switched to placebo for further 16 weeks. Kaplan-Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo and the hazard ratio for relapse (aripiprazole/placebo) was 0.57 (non-statistically significant difference). In this growing paediatric population, the mean weight gain over the stabilisation phase (up to 26 weeks) on aripiprazole was 3.2 kg, and a further mean increase of 2.2 kg for aripiprazole as compared to 0.6 kg for placebo was observed in the second phase (16 weeks) of the trial. Extrapyramidal symptoms were reported during the open stabilisation phase in 17% of patients, with tremor accounting for 6.5%. During the placebo substitution phase, extrapyramidal symptoms were equally reported in aripiprazole patients 3/39 (7.7%) and patients on placebo 3/43 (7.0%).

Applicant's Rationale for Changes:

The Applicant is in agreement to amend SmPC section 5.1 with information on study CN138-603.

Besides some editorial changes on the study design, the Applicant would like to clarify the proposed modifications related to the primary endpoint:

The relapse rates quoted of 32% for aripiprazole and 50% for placebo reported in the clinical study report (CSR) synopsis and Efficacy Results and Discussion sections of the CSR were mislabelled as Kaplan-Meier rates, when in fact they are the simple proportions (Number of Events/Number of Patients) from Table S.5.1. The simple proportions are not adjusted for censoring in the time from randomization to relapse analysis for the primary efficacy endpoint. The actual Kaplan-Meier relapse rates are estimated from the product-limit survival estimates at Week 16 from Table S.5.3. Kaplan-Meier rates are calculated

as 1 minus the proportion of subjects not experiencing relapse, which works out to 35% for aripiprazole and 52% for placebo. These Kaplan-Meier rates reflect the impact of censored observations in the estimates of probability of no relapse at a given point in time.

With regard to the observed weight gain the Applicant would like to highlight that given the investigated age range (6-17 years) this is a growing paediatric population.

Please note that the EPS rate (17%) reported during the open stabilisation phase corresponds to the overall randomised population and not just to the responder population from the subsequent double-blind placebo substitution phase.

Assessors comments:
It makes no sense to repeat the sentence *Aripiprazole was also studied in patients aged 6 to 17 ye*ars, because it is previously stated above. Moreover, it reports to this special autistic population, and not children in any indication. The string "long term study" is acceptable, since it follows the Guideline for long term studies in schizophrenia – the randomised withdrawal design is not accompanied by a description of a minimal duration to be considered a long term study.
The introduction *"In this growing paediatric population"* is compelling and induces readers to think that these children are growing and is therefore normal to put up 5,4 Kg within 32 to 40 weeks on aripiprazole treatment – and this is simply not the case. Therefore this must not be introduced.
The wording regarding Kaplan Meyer curve analysis is accepted, but the timeframe of relapse should be highlighted.
The sentence *"During the placebo substitution phase, extrapyramidal symptoms were equally reported in aripiprazole patients 3/39 (7.7%) and patients on placebo 3/43 (7.0%)"* may be misleading: in the second phase there was a selection bias, since the patients that had significant EPS in the stabilisation phase possibly did not continue to the substitution phase (there was a significant reduction in the sample from phase 1 to phase 2). Moreover, the 3 patients in each arm that constituted the 7.7 and 7.0% were described as "treatment emergent AEs", meaning that these were "de novo" EPS, and not patients continuing from one phase to the other with EPS. Therefore we propose not to include this statement.
In conclusion, it is proposed the text below:
Aripiprazole was also studied in a placebo-controlled, long-term maintenance trial. After a 13-26 week stabilisation on aripiprazole (2-15 mg/day) patients with a stable response were either maintained on aripiprazole or substituted to placebo for further 16 weeks. Kaplan-Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo; the hazard ratio for relapse within 16 weeks (aripiprazole/placebo) was 0.57 (non-statistically significant difference). The mean weight gain over the stabilisation phase (up to 26 weeks) on aripiprazole was 3.2 kg, and a further mean increase of 2.2 kg for aripiprazole as compared to 0.6 kg for placebo was observed in the second phase (16 weeks) of the trial. Extrapyramidal symptoms were mainly reported during the stabilisation phase in 17% of patients, with tremor accounting for 6.5%.

II. RAPPORTEUR'S OVERALL CONCLUSION AND FURTHER ACTION IF REQUIRED

This randomised withdrawal study for the study of maintenance of effect / possible rebound phenomena upon discontinuation of abilify in irritability associated with autistic disorder in children and adolescents ages 6 to 17 years old, requested by FDA as a post approval commitment did not raise new efficacy or safety concerns.

The study involved a population and indication not approved in Europe. Although no new safety issues have arisen in comparison with the AE profile of EU approved indications, there is information on Irritability associated with autistic disorder in the SPC that can be updated.
Therefore a change to SPC is proposed.
Regarding the cardiac effects and the changes in QTc since there was at least a case with QTc increase above > 30 msec, the MAH should continue monitoring effects on ECG and cardiac AEs and present the data in the PSURs.

PAC No. P46-065

Overall Conclusion:

The results from Study CN138603 do not change the paediatric or the overall benefit/risk profile of aripiprazole.

☒ PAC not fulfilled (all commitments fulfilled but further action required):

As outcome of this assessment, the MAH is requested to update the Product Information as follows and to submit the corresponding variation by one month:
Proposed changes to the SPC:

Section 5.1:
Where it reads:
"Irritability associated with autistic disorder in paediatric patients (see section 4.2):
Aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole."

Should read (appended text underlined):
"Irritability associated with autistic disorder in paediatric patients (see section 4.2):
Aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.
Aripiprazole was also studied in a placebo-controlled, long-term maintenance trial. After a 13-26 week stabilisation on aripiprazole (2-15 mg/day) patients with a stable response were either maintained on aripiprazole or substituted to placebo for further 16 weeks. Kaplan-Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo; the hazard ratio for relapse within 16 weeks

(aripiprazole/placebo) was 0.57 (non-statistically significant difference). The mean weight gain over the stabilisation phase (up to 26 weeks) on aripiprazole was 3.2 kg, and a further mean increase of 2.2 kg for aripiprazole as compared to 0.6 kg for placebo was observed in the second phase (16 weeks) of the trial. Extrapyramidal symptoms were mainly reported during the stabilisation phase in 17% of patients, with tremor accounting for 6.5%.

Note: no change is proposed to Section 4.2 Posology and method of administration.