Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Abilify®		
Name of Active Ingredient: Aripiprazole		

SYNOPSIS

Final Clinical Study Report for Study CN138502

ABBREVIATED REPORT

TITLE OF STUDY: A 12-week, Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Adjunctive Aripiprazole Therapy in the Treatment of Mania in Bipolar I Disorder Patients Treated with Valproate or Lithium and in Need of Further Clinical Improvement

INVESTIGATORS/STUDY CENTERS: 69 sites worldwide treated subjects

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 27-Jun-2008 **CLINICAL PHASE:** 3b

Study Completion Date: 05-Oct-2011

INTRODUCTION: Study CN138502 was designed to evaluate the efficacy and safety of adjunctive aripiprazole added to lithium or valproate treatment over a 12-week period in Bipolar I Disorder Mania subjects. In addition, secondary endpoints that have not been evaluated previously in a comparable study (CN138134) were included (e.g., subjects' functional outcome and subjects' treatment experience).

Due to the slow enrollment experienced over the last 12 months, the decision to stop recruitment was taken, and the last subject was enrolled on 03-Jun-2011; 370 subjects were randomized (181 in the adjunctive aripiprazole group and 189 in the adjunctive placebo group).

OBJECTIVES: Primary: To evaluate the efficacy of adjunctive treatment with aripiprazole compared to placebo, as measured by Young Mania Rating Scale (YMRS), in the treatment of Bipolar I Disorder Mania subjects treated with lithium and valproate and in need of further clinical improvement.

Secondary: To assess the effect of adjunctive treatment with aripiprazole compared to placebo in the same subject population in terms of:

- Efficacy, as measured on Clinical Global Impression - Bipolar Version (CGI-BP) Severity of Illness Score, response rate (≥ 50% improvement in YMRS Total Score), and remission rate (YMRS ≤ 12).

- Subject reported outcomes for Longitudinal Interval Follow-up Evaluation-Rating Impaired Functioning Tool (LIFE-RIFT) Score, Functional Assessment Short Test (FAST) Score, and Patient Global Impression Improvement (PGI-I) scale.
- Safety and tolerability, including the frequency and severity of adverse event (AE) and serious adverse event (SAE) reports, percentage of subjects with potentially clinically relevant changes in vital signs, routine laboratory tests and electrocardiograms (ECGs), and mean change from baseline in weight and the number and percentage of subjects with ≥ 7% increase or decrease in weight from baseline and median change from baseline in body mass index (BMI).

METHODOLOGY: This was a multicenter, randomized, double-blind, placebo-controlled study with 2 parallel groups of subjects. Eligible subjects were randomly assigned to receive either aripiprazole or placebo (1:1), adjunctive to their existing valproate or lithium treatment, for 12 weeks. Eligible subjects must have had a YMRS Total Score of ≥ 16 at screening and baseline and ≤ 35% decrease from screening visit assessed 14-28 days after the therapeutic serum level of valproate or lithium was confirmed.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 493 subjects were enrolled, and 370 were randomized (181 and 189 in the aripiprazole and placebo groups, respectively).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female subjects ≥ 18 years of age with a diagnosis of Bipolar I Mania (manic or mixed episode), as defined by DSM-IV-TR, on mood stabilizer (valproate or lithium) treatment were to be included. According to clinical judgment, and as defined by a YMRS Total Score ≥ 16, these subjects were selected for this study because they might have benefited from adjunctive treatment with aripiprazole.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: Ongoing mood stabilizers (lithium or valproate) were considered background therapy, and were not provided by Bristol-Myers Squibb. Subjects continued on their current valproate or lithium treatment.

Subjects received aripiprazole 5 mg/day for Week 1, the dose was up titrated to 10 mg/day for Weeks 2 and 3, and they received 15 mg/day for Weeks 4-6. Dosing was flexible (either 15 or 30 mg/day) for Weeks 7-12. During Weeks 7-12, the dose could be decreased to 10 mg/day due to tolerability reasons.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: All subjects continued to receive their usual doses of lithium or valproate. Subjects received a matching placebo and followed the same dosing schedule as the aripiprazole subjects in order to maintain the double-blind design of this study.

CRITERIA FOR EVALUATION: Efficacy: The primary efficacy measure was the mean change from baseline to endpoint (Week 12 LOCF) in YMRS Total Score. Other efficacy assessments included mean change from baseline to all time points in the CGI-BP Severity of Illness (mania, depression, overall) Score, response rate (≥ 50% improvement in YMRS Total Score) at all time points, remission rate (YMRS ≤ 12) at all time points, and the mean change from baseline to all other time points in YMRS Total Score.

Safety: Safety was assessed by the frequency and severity of AEs and SAEs, the percentage of subjects with potentially clinically relevant changes in vital signs, routine laboratory tests, and ECGs, the mean change from baseline in weight and the number and percentage of subjects with ≥ 7% increase or decrease in weight from baseline, and the median change from baseline in BMI.

Outcomes Research: Outcome assessments included mean change from baseline on the PGI-I scale, mean change from baseline to all time points in the FAST Score, and the mean change from baseline to all time points in LIFE-RIFT Score.

STATISTICAL CONSIDERATIONS: The primary endpoint was mean change from baseline to Week 12 in the YMRS Total Score, using the Efficacy Sample (last observation carried forward [LOCF]).

A total of 362 evaluable subjects (176 aripiprazole and 186 placebo) yields 77% power to detect a difference of 2.6 in the mean change from baseline in YMRS Score at Week 12 between adjunctive aripiprazole and placebo. The above calculations assumed a common standard deviation of 9.1, a 2-sided t-test for the difference between aripiprazole and placebo, and a 2-tailed 0.05 significance level.

The primary efficacy measure above was evaluated by an analysis of covariance (ANCOVA), with baseline Score as covariate and type of mood stabilizer (valproate or lithium) and treatment (aripiprazole versus placebo) as main effects.

Mean change from baseline in CGI-BP Severity of Illness and FAST Total Score and subscale scores were evaluated by an ANCOVA (LOCF and observed cases [OC]) using the Efficacy Sample, with baseline score as covariate and type of mood-stabilizer (valproate or lithium) and treatment (aripiprazole versus placebo) as main effects.

Testing of all the secondary endpoints were performed at the alpha = 0.05 significance level without adjustment for multiple comparisons.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: The majority of subjects completed the 12-week double-blind phase of the study (Table 1). The most common reason for discontinuation was AE.

Demographic characteristics for the Randomized Sample were comparable across treatment groups (Table 2). The majority of subjects were female and white, and the mean age was 44.7 years.

The mean baseline YMRS Total Score of the Randomized Sample was 23.3, indicative of a moderately-to-severely manic population. The mean baseline CGI-BP Severity of Illness Score (mania) for all randomized subjects was 4.2. Baseline assessment scores of psychiatric rating scales were comparable for the aripiprazole and placebo groups.

Table 1: Disposition of Subjects

Number of Subjects (%)

Subject Status	Placebo	Aripiprazole	Total
ENROLLED	-	-	493
RANDOMIZED	189	181	370
DISCONTINUED DURING DOUBLE-BLIND PHASE (a)	58 (30.7)	59 (32.6)	117 (31.6)
LACK OF EFFICACY	11 (5.8)	10 (5.5)	21 (5.7)
ADVERSE EVENT	25 (13.2)	23 (12.7)	48 (13.0)
PATIENT WITHDREW CONSENT	11 (5.8)	14 (7.7)	25 (6.8)
LOST TO FOLLOW-UP	3 (1.6)	5 (2.8)	8 (2.2)
POOR/NON-COMPLIANCE	3 (1.6)	5 (2.8)	8 (2.2)
PREGNANCY	1 (0.5)	0	1 (0.3)
PATIENT NO LONGER MEETS STUDY CRITERIA	0	1 (0.6)	1 (0.3)
OTHER	4 (2.1)	1 (0.6)	5 (1.4)
COMPLETED 12-WEEK DOUBLE-BLIND PHASE (a)	131 (69.3)	122 (67.4)	253 (68.4)

(a) Percentages are based on the number of patients randomized using the randomized treatment.

Table 2: Demographic Characteristics, Randomized Sample

	Placebo N = 189	Aripiprazole N = 181	Total N = 370
AGE (YEARS)			
MEAN	44.92	44.37	44.65
MEDIAN	46.00	44.00	45.00
MIN-MAX	18.00-70.00	18.00-73.00	18.00-73.00
S.D.	12.99	12.13	12.57
GENDER, N (%)			
MALE	90 (48)	80 (44)	170 (46)
FEMALE	99 (52)	101 (56)	200 (54)
RACE, N (%)			
WHITE	179 (95)	172 (95)	351 (95)
BLACK/AFRICAN AMERICAN	6 (3)	6 (3)	12 (3)
ASIAN	1 (1)	2 (1)	3 (1)
OTHER	3 (2)	1 (1)	4 (1)
WEIGHT (KG)			
MEAN	77.9	79.9	78.9
MEDIAN	78.0	78.5	78.0
MIN-MAX	45.0-135.0	46.0-163.0	45.0-163.0
S.D.	14.9	17.1	16.0
MISSING	1	1	2
BMI (KG/M**2)			
MEAN	27.3	28.3	27.7
MEDIAN	26.3	27.2	26.5
MIN-MAX	18.0-44.6	17.1-62.1	17.1-62.1
S.D.	4.7	6.1	5.4
MISSING	1	2	3

Efficacy Results: For the primary efficacy endpoint, the mean change from baseline to Week 12 in the YMRS Total Score (LOCF), aripiprazole added to lithium or valproate did not show statistically significantly improvement compared with placebo added to lithium or valproate; the treatment difference was -2.04 in favor of aripiprazole (95% confidence interval [CI]: -4.14, 0.07; P = 0.058).

For the key secondary efficacy endpoint, the mean change from baseline to Week 12 in CGI-BP Severity of Illness Score (mania) (LOCF), the treatment difference was -0.30 points in favor of aripiprazole compared with placebo (95% CI: -0.59, -0.01).

At Week 12, 69.9% of aripiprazole-treated subjects and 61.3% of placebo-treated subjects had a response, and 68.8% of aripiprazole-treated subjects and 64.0% of placebo-treated subjects were in remission.

Safety Results: One death was reported in subject treated with aripiprazole and lithium (acute respiratory failure after falling into a coma) that was not considered related to the study therapy by the investigator. Treatment-emergent SAEs were reported for 6.1% and 9.0% of subjects in the aripiprazole and placebo groups, respectively, and the most frequently reported SAEs were psychiatric disorders (5.0% and 5.8% in the aripiprazole and placebo groups, respectively).

The incidence of treatment-emergent AEs that led to discontinuation of study therapy was comparable in the aripiprazole and placebo groups (12.8% and 13.2%, respectively). The most frequently reported AEs leading to discontinuation of study therapy were depression (5.6%) and akathisia (3.9%) in the aripiprazole group and mania (4.2%) in the placebo group.

The incidence of treatment-emergent AEs was higher in the aripiprazole group (52.8%) than in the placebo group (40.2%). Treatment-emergent AEs that were reported with an incidence of ≥ 5% in the aripiprazole group and at least twice the rate of placebo were akathisia (11.1% vs 2.1%), depression (9.4% vs 3.2%), and nausea (5.6% vs 2.6%).

The incidence of treatment-emergent EPS-related AEs was higher in the aripiprazole group (17.2%) than in the placebo group (3.7%). The most frequently reported event was akathisia (11.1% and 2.1% in the aripiprazole and placebo groups, respectively).

The incidence of potentially clinically relevant laboratory abnormalities was comparable between treatment groups, with the exception of fasting triglycerides (46.1% and 30.6% in the aripiprazole and placebo groups, respectively).

The most frequently reported potentially clinically relevant ECG abnormality was QTC prolongation (Bazett) (8.1% and 12.5% in the aripiprazole and placebo groups, respectively). There was no statistically significant treatment difference between the 2 treatment groups in median change in any ECG measurement from baseline to Week 12.

The incidence of potentially clinically relevant vital sign abnormalities was low and comparable between treatment groups.

There was no statistically significant treatment difference between treatment groups in mean weight change from baseline to Week 12 (LOCF), clinically relevant weight gain or loss (≥ 7% vs baseline), or median change from baseline to Week 12 (LOCF) in BMI.

Outcomes Research Results: There was an improvement in adjusted mean change from baseline to Week 12 in the LIFE-RIFT Total Score (OC dataset) favoring placebo (treatment difference 0.61; 95% CI: -0.13, 1.34).

The adjusted mean change from baseline to Week 12 (LOCF), in FAST Total Score was better in the placebo group than in the aripiprazole group (treatment difference 1.88; 95% CI: -1.08, 4.84). At Week 12, a greater improvement with placebo was also observed in cognitive functioning compared with aripiprazole (treatment difference 0.68; 95% CI: -0.06, 1.42).

There was no difference between treatment groups in adjusted mean change from baseline to Week 12 in the PGI-I scale (OC dataset).

CONCLUSIONS:

- The target sample size of 388 subjects was not achieved in this study; 370 subjects were randomized (181 in the aripiprazole group and 189 in the placebo group).
- The primary endpoint was mean change from baseline to Week 12 (LOCF) in the YMRS Total Score. Aripiprazole plus lithium or valproate did not achieve statistical significance vs placebo plus lithium or valproate at Week 12 in the change in YMRS (treatment difference of 2.04 points in favor of aripiprazole, P=0.058). Although differences between treatment groups increased over time, a treatment difference favoring aripiprazole was observed only at Week 9 (-2.37; 95% CI: -4.40, -0.34).
- The mean change from baseline to Week 12 (LOCF) in the CGI-BP Severity of Illness (mania) Score favored aripiprazole (treatment difference of 0.30; 95% CI: -0.59, -0.01).
- At Week 12, the remission rate was comparable in both treatment groups.
- At Week 12, no differences between treatment groups were seen in the LIFE-RIFT Total Score and in the FAST Total Score.
- No new or unexpected AEs occurred. The most common AEs were akathisia, depression, insomnia, nausea, and headache. Comparable discontinuation rates were observed in both groups (aripiprazole 12.8% vs placebo 13.2%). The most common AEs that led to discontinuation were depression (aripiprazole 5.6% vs placebo 2.1 %) and akathisia (aripiprazole 3.9% vs placebo 0.5%). Comparable completion rates were seen in both treatment groups.

DATE OF REPORT: 11-May-2012