CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-436/S029, 21-729/S014, 21-713/S021, 21-866/S016
Priority or Standard	S
Submit Date(s)	04/16/2010
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PDUFA Goal Date	02/16/2011
Division / Office	DPP-130
Reviewer Name(s)	Maju Mathews, MD
Review Completion Date	01/12/2011
Established Name	Aripiprazole
(Proposed) Trade Name	ABILIFY
Therapeutic Class	Atypical antipsychotic
Applicant	Bristol-Myers Squibb
Formulation(s)	5, 10, 15 and 30 mg
Dosing Regimen	
Indication(s)	Adjunctive treatment of Bipolar Disorder
Intended Population(s)	Adults with Bipolar Disorder

Template Version: March 4, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that the Division of Psychiatry Products take an approval action for NDA supplements 21-436/S029, 21-729/S014, 21-713/S021, 21-866/S016. In my opinion, the sponsor has demonstrated the efficacy and safety of ABILIFY in combination with lithium or valproate as long term maintenance therapy for patients with bipolar I disorder, manic or mixed, with or without psychotic features. The sponsor conducted one study, CN138189, which was an adequate and well controlled trial that demonstrated the efficacy of ABILIFY as measured by time from randomization to relapse to any mood episode. There was a statistically and clinically significant difference in the treatment effect of ABILIFY in combination with lithium or valproate compared to placebo in combination with lithium or valproate.

In my opinion, treatment with ABILIFY was reasonably safe and well tolerated.

Labeling recommendations have been made. Please refer to section 9.2 Labeling Recommendations for detailed comments. Final approval is contingent on satisfactory response to the agency's recommendations and mutual agreement on labeling as well as the conclusions of the CMC, pharmacology/toxicology, and clinical pharmacology reviewers.

1.2 Risk Benefit Assessment

Bipolar I Disorder is a lifelong episodic illness characterized by manic or depressive episodes followed by symptom-free periods. Psychotic symptoms often accompany the manic phase of bipolar disorder.

The lifetime prevalence of bipolar disorder is estimated to be 0.4% to 1.6%. The mean age at onset for a first manic episode is the early 20's. Lithium and valproate are often recommended as treatments for manic symptoms associated with bipolar disorder. However, a substantial number of patients fail to respond to these medications. When monotherapy fails, the guidelines recommend combination therapies.

Aripiprazole is currently approved as monotherapy for the short-term and maintenance treatment of patients with Bipolar I Disorder (manic or mixed episodes). In addition, aripiprazole is approved for short-term use (6 weeks) as adjunctive treatment with lithium or valproate in this population.

The safety profile of ABILIFY is similar to other available atypical antipsychotics. ABILIFY has been available on the market since 2002. It is a widely used antipsychotic. In my opinion, the benefits of treatment with ABILIFY generally outweigh the risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

ABILIFY is currently approved for the treatment of schizophrenia, bipolar disorder and adjunctive treatment of depression. No new safety concerns were identified during this review. Risk evaluation and mitigation strategies are not indicated at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

ABILIFY (aripiprazole), a dihydrocarbostyril (quinolinone) derivative, was discovered

by Otsuka Pharmaceutical Co, Ltd (OPC) and was developed collaboratively by OPC and Bristol-Myers Squibb Company. Aripiprazole's efficacy in schizophrenia and bipolar disorder is thought to be mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are a number of drugs approved for the treatment of bipolar disorder. These fall under the categories of antipsychotics and mood stabilizers.

Table 1: Currently Approved Antipsychotic Drugs

Antipsychotics	Mood Stabilizers
Aripiprazole Clozapine Ziprazodone Risperidone Asenapine Quetiapine Olanzapine	Lithium Valproic Acid Lamotrigine Carbamazepine

2.3 Availability of Proposed Active Ingredient in the United States

ABILIFY (aripiprazole) tablets are approved in the U.S and Europe and many other countries for the treatment of schizophrenia and bipolar disorder. The original NDA submission was approved in November 2002.

2.4 Important Safety Issues With Consideration to Related Drugs

Aripiprazole belongs to the category of atypical antipsychotics. It is a partial dopamine agonist. However, it shares many adverse effects commonly seen with dopamine antagonists like extrapyramidal symptoms including akathisia, rigidity, tremors, and weight gain coupled with metabolic syndrome.

These safety concerns have been addressed in the labeling of aripiprazole. There are no new safety issues that have been generated in this submission.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Aripiprazole was approved in the U.S. as monotherapy for treatment of acute manic or mixed episodes associated with Bipolar Disorder in September 2004 (S-002). Upon approval of this application, BMS/Otsuka agreed to the post-approval commitment listed below.

- *Clinical Efficacy and Safety: Adult clinical study to address longer-term efficacy and safety of aripiprazole as add-on therapy in bipolar disorder.*

The study report was submitted to fulfill the PAC on September 28, 2009.

A pre-sNDA meeting request was submitted December 1, 2009.

Preliminary responses were received from FDA on February 16, 2010.

BMS/Otsuka sent clarification questions on February 22, 2010, FDA responded on February 24, 2010, and the pre-sNDA meeting was subsequently cancelled.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of submission was adequate.

3.2 Compliance with Good Clinical Practices

This study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The protocol, amendments, and

patient informed consent received appropriate approval by the IRB/IEC prior to initiation of the study at the site.

The majority of investigators attended an investigator meeting held in 4 regions (United States [US], Europe, India, and Brazil). Investigators and their staff were trained by BMS, or its designee ((b) (4) regarding regulations, company procedures in the conduct of clinical research with investigational agents, protocol design, and study logistics. An initiation visit was held at every non-US site and any US site that did not attend an investigator's meeting. Site Monitoring visits were conducted at least every 8 weeks while patients were in Phase 1 and 2. When subjects were in Phase 3, a site visit was conducted approximately every 12 weeks. Patient enrollment at each center and receipt of critical case report forms (CRFs) were verified. A data edit program was run to check item ranges, missing values, and relational events. All critical data values were verified for consistency after correcting for transcription, data entry, and coding errors. CRFs were reviewed by a data manager from (b) (4). Data were entered using Oracle Clinical software and double-entry procedures based on a clinical algorithm.

The Division of Scientific Investigations (DSI) conducted site visits at the sites listed in the Table below.

Table 2: List of Sites Inspected by the Division of Scientific Investigations.

Name of CI	City, State	Protocol/Study Site	Insp. Date
Arifulla Khan, MD	Bellevue, WA	CN 138189 Site #123	August 9-24, 2010
Sandra Ruschel, MD	Rio de Janeiro, Brazil	CN 138189 Site #65	November 8-12, 2010
Joao Alberto Campos, MD	Goias, Brazil	CN 138189 Site #88	August 23-27, 2010
Bristol-Myers Squibb	Wallingford, CT	Sponsor	November 22-26, 2010

The review division (DSI) concluded that '*As part of the PDUFA-related inspections, a single U.S. and two Brazilian clinical investigator sites were inspected in support of this application. Minor regulatory violations were noted at the clinical sites, which are unlikely to have a significant impact on data integrity and human subject safety protection. Sponsor was also inspected due to issues that were clarified ultimately regarding clinical site #88.*

The inspection documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations, and the data are considered reliable in support of the application.'

Reviewers Comments: I concur with the conclusion of the DSI Inspection review.

3.3 Financial Disclosures

The sponsor requested statements of financial interests and arrangements from a total of 87 investigators and 353 sub-investigators. As of Feb 22, 2010, 87 statements of the 87 investigators were received and 347 of 353 sub-investigators were received, none of which had disclosable information. Of the six missing sub-investigator statements, one had a wrong name, and the correct person was identified, two did not participate in the studies, one left the site in 2006 and two have not yet provided the requested information.

Reviewer's Comments: I do not believe that the missing financial disclosures affect the reliability and integrity of the results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

No new data was submitted.

4.4 Clinical Pharmacology

No new data submitted

4.4.1 Mechanism of Action

4.4.2 Pharmacodynamics

Aripiprazole is a partial agonist at dopamine D2 receptors. Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, $alpha_1$-adrenergic and histamine H_1 receptors (K_i values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K_i=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50}>1000 nM). Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor. These pharmacologic properties are predictive of antidepressant activity.

4.4.3 Pharmacokinetics

The action of ABILIFY is primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D_2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady-state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3: Clinical Study in Current Submission.

Type of Study	Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects/ Discontinuations due to AEs	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase IIIB/IV Efficacy	CN138189	To evaluate the efficacy of aripiprazole in combination with lithium or valproate, compared with placebo in combination with lithium or valproate, as long-term maintenance therapy for patients with Bipolar I Disorder, manic or mixed, with or without psychotic features, demonstrating	Multicenter, Randomized, Double-blind, Placebo-controlled 3 Phases: Phase 1: Screening and Confirmation of Partial Non-Response Phase 2: Stability and Maintenance of Stability Phase 3: Relapse Assessment Country	Phase 2: Stability and Maintenance of Stability Aripiprazole 10mg / 15 mg / 30 mg once daily; Oral Phase 3: Relapse Assessment Aripiprazole 10mg / 15 mg / 30 mg once daily; Oral	1270 enrolled / 34 subjects discontinued due to AEs in Phase 3	Subjects with Bipolar I Disorder, manic or mixed, with or without psychosis	Phase 1: 2 - 8 weeks; Mood Stabilizer (Lithium or Valproate) per local country guidelines Phase 2: 13 - 24 weeks: Mood Stabilizer in combination with single-blind aripiprazole Phase 3: 52 weeks; Mood Stabilizer in combination with double-blind aripiprazole or placebo	Completed; Full Extension Phase (India Only): Completed; Synoptic Report in Process

5.2 Review Strategy

Review of efficacy and safety consisted of review of study reports of CN138189.

Table 4: Listing of items reviewed.

Submission Date	Items reviewed
04/16/2010	• Clinical Study Reports CN138189 • Application summary • Proposed labeling • Financial information • Case report Froms

5.3 Discussion of Individual Studies/Clinical Trials

A detailed discussion of the study is under the review of efficacy.

6 Review of Efficacy

The sponsor conducted one long term maintenance study, CN138189 to study the efficacy of aripiprazole in combination with lithium or valproate in the long term treatment of mania in patients with bipolar disorder partially nonresponsive to lithium or valproate monotherapy. This study was a multicenter, double-blind, placebo-controlled, outpatient study with 2-parallel treatment groups. The study was conducted in three phases and the primary endpoint was time from randomization to Phase 3 to relapse to any mood episode. There were 88 investigators in 8 countries (Brazil, Croatia, Czech Republic, France, India, Russian Federation, South Africa, and the United States) who participated in the study. The study began on 29-September-2005 and ended on 2-June-2009.

Efficacy Summary

Title of Study: Efficacy of Aripiprazole in Combination with Lithium or Valproate in the Long Term Treatment of Mania in Patients with Bipolar I Disorder Partially Non-responsive to Lithium or Valproate Monotherapy.

Indication

Long term treatment of mania in patients with bipolar I disorder partially nonresponsive to lithium or valproate monotherapy.

Design/Objectives/Methods

Design

This was a multicenter, randomized, double-blind, placebo-controlled outpatient study with 2 parallel treatment groups. Approximately 1270 patients, with Bipolar I Disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and confirmed by the Structured Clinical Interview for DSM IV (SCID) who displayed an acute manic or mixed episode with or without psychotic features and a minimum severity defined by a Young-Mania Rating Scale (Y-MRS) Score of ≥ 16 were considered for this study.

The study consisted of 3 phases:

- Phase 1: Screening, washout and confirmation of partial non-response phase (2 to 8 weeks)
- Phase 2: Stability and maintenance of stability phase (13 to 24 weeks)
- Phase 3: Assessment of relapse phase (52 weeks)

In Phase 1, patients with acute manic or mixed symptomatology were assigned to a mood stabilizer of the investigator's choice, either lithium or valproate. Patients who were currently receiving lithium or valproate were also eligible for the study if their symptoms met entry criteria.

Two weeks after confirmation of a therapeutic level (lithium: 0.6 - 1.0 mmol/L or valproate 50 - 125 µg/ml) patients with a partial non-response (Y-MRS ≥ 16) to treatment with mood stabilizer monotherapy were eligible to enter Phase 2, where aripiprazole (10 to 30 mg/day; starting dose: 15 mg/day) was assigned in a single-blind fashion.

Patients responding to the combination of aripiprazole and mood stabilizer, and maintaining response for 12 weeks (with 1 excursion [defined as a YMRS and/or Montgomery Asberg Depression Rating Scale (MADRS) Score at a given visit of > 12] allowed, except at the last visit), were eligible for Phase 3.

In Phase 3, 337 patients were randomized in a double-blind fashion to continuation of aripiprazole (10 to 30 mg/day [starting dose: that prescribed as of the end of Phase 2]) plus mood stabilizer or placebo plus mood stabilizer in a 1:1 ratio. Patients were then followed for a maximum of 52 weeks, or until a relapse occurred.

Criteria for relapse included 1 or more of the following:

- Hospitalization for a manic, mixed or depressive episode.
- Serious adverse event of worsening disease under study accompanied by a Y-MRS > 16 and/or a MADRS > 16.
- Discontinuation due to lack of efficacy as determined by the investigator accompanied by a Y-MRS > 16 and/or a MADRS > 16.

Objectives

Primary

To evaluate the efficacy of aripiprazole in combination with lithium or valproate, compared with placebo in combination with lithium or valproate, as long-term maintenance therapy for patients with Bipolar I Disorder, manic or mixed, with or without psychotic features, demonstrating maintenance of stability for a minimum of 12 weeks when treated with aripiprazole in combination with lithium or valproate, as measured by the time to relapse.

Secondary

To evaluate the safety and tolerability of aripiprazole in combination with lithium or valproate as long-term maintenance therapy in this same patient population.

Key Inclusion Criteria

Patients meeting DSM-IV-TR criteria for Bipolar I Disorder, who displayed an acute manic or mixed episode with or without psychotic features, as confirmed by the SCID; rapid cyclers with < 7 mood episodes in the last year were included.

Patients with a Y-MRS Total Score of ≥ 16 at the Screening Visit.

Patients with a history of 1 or more manic or mixed episodes of sufficient severity to require hospitalization and/or treatment with a mood stabilizer or antipsychotic.

Men and women, ≥ 18 years of age.

Inclusion Criteria during Phase 1

Patients with an adequate washout of prohibited concomitant medications.

Patients with lithium or valproate serum levels within therapeutic range (lithium: 0.6 - 1.0 mmol/l or valproate: 50 - 125 µg/ml).

Patients with a Y-MRS Total Score of ≥ 16 two weeks after therapeutic levels of mood stabilizer were achieved, with no more than a 35% decrease from the initial Y-MRS assessment; an increased or unchanged Y-MRS Score was also allowed.

Inclusion Criteria assessed prior to Entry into Phase 3

Patients whose bipolar disorder was stable as evidenced by:

- Y-MRS Total Score and MADRS Total Score that has been ≤ 12 for at least 12 weeks, with a maximum of 1 excursion (defined as a Y-MRS Total Score > 12

and/or a MADRS Total Score > 12) in the intervening interval

- Y-MRS and a MADRS Total Score of ≤ 12 at the final Phase 2 visit

Key Exclusion Criteria

Women of child bearing potential who are unwilling or unable to use an acceptable method of birth control, using a prohibited contraceptive method, become pregnant or are breastfeeding.

Patients with current diagnosis of delirium, dementia, cognitive disorders, paranoid, schizotypal, schizoid, or antisocial personality disorder.

Patients with current Axis I diagnosis of bipolar II disorder, rapid cyclers experiencing 7 or more mood episodes within the past year, patients with first manic episode or current manic or mixed episode with a duration >2 years, and treatment refractory patients.

Patients at significant risk of committing suicide and those who currently meet criteria for substance abuse or dependence.

Exclusion Criteria Prior to Entry into Phase 2

Patients on mood stabilizers other than lithium or valproate within 2 weeks of entry into Phase 2.

Patients who had received antidepressants within 2 weeks prior to entry into Phase 2 (6 weeks for fluoxetine or Symbyax™).

Recent treatment of the most recent manic or mixed acute episode with a long-acting

antipsychotic in which the last dose was less than 1 full dosing interval plus 3 weeks prior to entering Phase 2.

Electroconvulsive therapy (ECT) treatment during the current episode or within 3 months prior to entry into Phase 2.

Exclusion Criteria Assessed Prior to Entry into Phase 3

Patients who had not responded to combination therapy by Week 12 of Phase 2.

Patients who had more than 1 mood excursion after achieving a response to combination therapy at a point in the trial where they would not be able to maintain stability for a minimum of 12 weeks without exceeding 24 total weeks in Phase 2.

Doses and Administration

Patients were administered a mood stabilizer (ie, lithium or valproate) during Phase 1 and throughout the study. Patients were additionally administered single-blind aripiprazole (10 to 30 mg/day; starting dose: 15 mg/day) during Phase 2 and randomized, using a 1:1 (aripiprazole:placebo) scheme, to 1 of 2 treatment groups upon entering Phase 3:

- Double-blind aripiprazole 10 to 30 mg/day (starting dose: that prescribed as of the end of Phase 2) co-administered with open-label lithium or valproate
- Double-blind placebo co-administered with open-label lithium or valproate.

Doses of lithium or valproate were adjusted to maintain therapeutic serum levels (ie, lithium: 0.6 - 1.0 mmol/l or valproate: 50 - 125 µg/ml), which were assessed approximately every 5 to 7 days (approximately 10 to 14 hours after the last dose).

Patients who could not tolerate the lowest dose possible of lithium or valproate at therapeutic levels were discontinued from the study. Patients were not allowed to change mood stabilizers (lithium or valproate) after they had enrolled in the study.

For patients receiving aripiprazole (singe-blind in Phase 2 or double-blind in Phase 3), tablets contained either 10 mg or 15 mg of aripiprazole. All patients initially took one 15-mg tablet per day. From Day 4 of Phase 2 onward throughout the remainder of the study, investigators could have increased the aripiprazole dose to two 15-mg tablets per day (ie, 30 mg/day of aripiprazole or 2 tablets of aripiprazole matching placebo during Phase 3) to maximize clinical response. Investigators could also have decreased the aripiprazole dose, starting on Day 4 of Phase 2 onward throughout the study, to one 10-mg tablet per day. Patients were to always be receiving 10, 15, or 30 mg of aripiprazole. The dose of aripiprazole initially assigned in Phase 3 was the same as the dose taken on the last day of Phase 2. For patients randomized to placebo in Phase 3, all tablets were inactive for the duration of the double blind phase.

Study medication was administered orally at approximately the same time each day without regard to meals.

Blinding

During the entire study, treatment with a mood stabilizer (ie, lithium or valproate) was open-label meaning the investigator and patient had knowledge of the assigned treatment.

During Phase 2 (Stability and Maintenance of Stability Phase), treatment with aripiprazole was single-blind, meaning the investigator, but not the patient, had knowledge of the treatment assignment to aripiprazole.

The treatment code for aripiprazole and placebo during Phase 3 (Assessment of Relapse Phase) was double-blind, meaning that neither the investigator nor the patient had knowledge of the treatment assignment.

Primary Endpoint

The primary endpoint was time from randomization to relapse of any mood episode. Time from randomization to relapse was calculated as date of relapse - date of randomization +1.

Key Secondary Endpoint

The key secondary efficacy variable was the mean change from baseline (end of Phase 2) to endpoint (Week 52, LOCF) in the Clinical Global Impression-Bipolar Version (CGI-BP) Severity of Illness Score (mania).

Other secondary efficacy endpoints include mean change from baseline in the Y-MRS & MADRS total scores, CGI-BP severity of illness overall and depression scores. Mean CGI-BP change from preceding phase score, percentage of patients maintaining remission during Phase 3 (Y-MRS & MADRS total scores <12), and time from randomization to relapse of manic and depressive episode.

Number of Patients

A total of 1270 patients were enrolled in the study. 337 patients were randomized to double blind treatment.

Statistical Analyses

The primary efficacy measure was the time from randomization to relapse of any mood

episode. The primary efficacy outcome measure was evaluated by 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, controlling for type of mood stabilizer (lithium or valproate) and type of index mood episode (manic or mixed). Patients who had not relapsed, including those patients who discontinued early for reasons other than relapse, were censored on their date of last efficacy evaluation or their last dose of study medication, whichever was later. Any randomized patient who was never treated and did not experience an event were censored on their randomization date. The estimated hazard ratio and 95% confidence interval (CI) were obtained from the Cox regression model, with type of mood stabilizer and type of index mood episode as stratification factors and with treatment group as covariate.

The key secondary efficacy outcome measure was the mean change from baseline (end of Phase 2) to endpoint (Week 52 LOCF) in the CGI-BP Severity of Illness Score (mania). For the key secondary analysis, a hierarchical testing procedure was used so that the overall experiment-wise type I error rate was 0.05.

Time from randomization to relapse of manic episode and time from randomization to relapse of depressive episode was evaluated by survival analysis using the Randomized Sample. The mean change from end of Phase 2 in the Y-MRS Total Score, MADRS Total Score, CGI-BP Severity of Illness Score (overall), and CGI-BP Severity of Illness Score (depression) was evaluated using ANCOVA.

Safety

Safety and tolerability of study medication was evaluated by reports of AEs and potentially clinically significant changes in ECGs, vital signs, and laboratory tests. The incidence of AEs was tabulated according to severity and drug-attributability. The mean change from baseline (end of Phase 2) in patient weight and the number and

percentage of patients with ≥ 7% increase or decrease in weight from baseline were evaluated by study week, mood stabilizer type, and treatment group. The mean change from baseline in serum prolactin was also evaluated. A secondary analysis was performed on patient weight and serum prolactin where the worst value observed during Phase 3 was used to determine the change from baseline score.

Safety and tolerance were also evaluated by the mean change from end of Phase 2 in the AIMS Total Score (sum of Items 1 to 7), SAS 10-item Total Score, and Barnes Global Clinical Assessment of akathisia item.

All safety analyses were performed on the Safety Sample, and were presented by mood stabilizer type and treatment. For safety analyses, patients were analyzed as treated.

Results

Demographics

The mean age of the randomized patients was 39 years; 54.9% were female and 68.2% were white. Demographic characteristics were similar between the two groups.

Table 5: Demographic Characteristics of Subjects Enrolled in Study

	Placebo N = 169	Aripiprazole N = 168	Overall N = 337
Age (years)			
Mean (SD)	38.8 (12.29)	39.2 (12.43)	39.0 (12.34)
Range	18 - 74	18 - 69	18 - 74
Gender, n (%)			
Male	71 (42.0)	81 (48.2)	152 (45.1)
Female	98 (58.0)	87 (51.8)	185 (54.9)
Race, n (%)			
White	112 (66.3)	118 (70.2)	230 (68.2)
Black	19 (11.2)	12 (7.1)	31 (9.2)
Asian	33 (19.5)	34 (20.2)	67 (19.9)
Other	5 (3.0)	4 (2.4)	9 (2.7)
Weight (kg)			
Mean (SD)	81.3 (25.11)	80.6 (18.89)	81.0 (22.20)
Range	44 - 181	46 - 144	44 - 181
Body Mass Index (kg/m^2)			
Mean (SD)	28.7 (7.72)	28.5 (6.00)	28.6 (6.90)
Range	17 - 61	19 - 53	17 - 61

Mean Y-MRS, CGI-BP, and MADRS baseline ratings were similar between treatment groups.

6.1. 3 Subject Disposition

A total of 1270 patients were enrolled in Phase 1 of the study (Screening, Washout and Confirmation of Partial Nonresponse Phase), 686 (54.0%) completed this phase and 584 (46.0%) were screen failures or discontinued during Phase 1, with the most common reasons being patient no longer met study criteria for various reasons (24.2%), lost to follow up (8.7%), and patient withdrew consent (7.3%).

Among the 686 patients who entered Phase 2 (Single-blind Stabilization Phase), 346 (50.4%) completed this phase and 340 (49.6%) discontinued during Phase 2. The most common reasons for discontinuation from Phase 2 were due to AE (13.6%), withdrawal of consent (9.5%), and patient lost to follow up (8.6%).

Of the 346 patients who completed Phase 2, 337 patients were randomized to double-blind treatment in Phase 3 (Assessment of Relapse Phase). The 9 patients who were not randomized discontinued for mood symptoms according to the CRF mood status page. A total of 192 (57.0%) of the 337 patients completed the 52-week double-blind phase of the study and 145 (43.0%) discontinued from Phase 3 of the study: 80 (47.3%) placebo-treated patients and 65 (38.7%) aripiprazole-treated patients.

The 3 most common reasons for discontinuing from aripiprazole therapy were due to AE (11.3%), withdrawal of consent (8.9%), and lack of efficacy (8.3%); and for discontinuing from placebo therapy, the 3 most common reasons were due to lack of efficacy (18.3%), AE (8.9%), and withdrawal of consent (8.3%). Among randomized patients, the rate of discontinuation for mood symptoms (manic, depressive, or mixed) was higher in the placebo group than in the aripiprazole group.

Table 6: Disposition of Study Subjects

	Number of Patients (%)		
Patient Status	Placebo	Aripiprazole	Total
ENROLLED	---	---	1270
SCREEN FAILURE OR DISCONTINUED DURING PHASE 1 (a)	---	---	584 (46.0)
ADVERSE EVENT	---	---	33 (2.6)
SUBJECT WITHDREW CONSENT	---	---	93 (7.3)
LOST TO FOLLOW-UP	---	---	111 (8.7)
POOR/NON-COMPLIANCE	---	---	23 (1.8)
PREGNANCY	---	---	1 (0.1)
SUBJECT NO LONGER MEETS STUDY CRITERIA	---	---	307 (24.2)
OTHER	---	---	16 (1.3)
COMPLETED PHASE 1 AND ENTERED PHASE 2 (a)	---	---	686 (54.0)
DISCONTINUED DURING PHASE 2 (b)	---	---	340 (49.6)
LACK OF EFFICACY	---	---	43 (6.3)
ADVERSE EVENT	---	---	93 (13.6)
SUBJECT WITHDREW CONSENT	---	---	65 (9.5)
LOST TO FOLLOW-UP	---	---	59 (8.6)
POOR/NON-COMPLIANCE	---	---	33 (4.8)
PREGNANCY	---	---	1 (0.1)
SUBJECT NO LONGER MEETS STUDY CRITERIA	---	---	32 (4.7)
ADMINISTRATIVE REASON BY SPONSOR	---	---	1 (0.1)
OTHER	---	---	13 (1.9)
COMPLETED PHASE 2 (b)	---	---	346 (50.4)
RANDOMIZED	169	168	337

DISCONTINUED 52-WEEK DOUBLE-BLIND PHASE (c)	80 (47.3)	65 (38.7)	145 (43.0)
LACK OF EFFICACY	31 (18.3)	14 (8.3)	45 (13.4)
ADVERSE EVENT	15 (8.9)	19 (11.3)	34 (10.1)
SUBJECT WITHDREW CONSENT	14 (8.3)	15 (8.9)	29 (8.6)
DEATH	0	1 (0.6)	1 (0.3)
LOST TO FOLLOW-UP	7 (4.1)	6 (3.6)	13 (3.9)
POOR/NON-COMPLIANCE	5 (3.0)	3 (1.8)	8 (2.4)
PREGNANCY	2 (1.2)	1 (0.6)	3 (0.9)
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (1.2)	1 (0.6)	3 (0.9)
ADMINISTRATIVE REASON BY SPONSOR	0	2 (1.2)	2 (0.6)
OTHER	4 (2.4)	3 (1.8)	7 (2.1)
COMPLETED 52-WEEK DOUBLE-BLIND PHASE (c)	89 (52.7)	103 (61.3)	192 (57.0)

Protocol Violations

There were a number of protocol violations that could potentially affect the interpretability of study results. The most frequent reasons for protocol deviations during Phase 3 of the study were: mood stabilizer noncompliance (< 80% days with drug administered or dosing gaps of > 4 consecutive days; placebo 21/166 [12.7%], aripiprazole 20/167 [12.0%]; Safety Sample) and use of prohibited medications (primarily anticholinergics, anxiolytics, and antihistamines) on or after the randomization date (placebo 21/169 [12.4%], aripiprazole 20/168 [11.9%]; Randomized Sample). Another protocol violation involved patients randomized without previous manic episode of sufficient severity to require hospitalization and/or treatment with mood stabilizer, placebo 15 vs aripiprazole 7.

Concomitant Medication Use

Approximately 70% of patients in either treatment group took at least 1 CNS medication during Phase 3. The most common class of concomitant CNS medication used during Phase 3 was anxiolytics for both treatment groups, and the most common class used during Phase 2 was also anxiolytics for both treatment groups. Results were similar when analyzed by type of mood stabilizer. For the potential treatment of EPS, the most common concomitant medication used during Phase 3 in both treatment groups was propranolol.

Table 7: Summary of Concomitaant Medications During Phase 3, Phase 3 Safety Sample.

BODY SYSTEM CONCOMITANT MEDICATION	Number(%) of Patients Placebo N=166	 Aripiprazole N=167
ANY CNS MEDICATIONS	115 (69.3)	118 (70.7)
NERVOUS SYSTEM	115 (69.3)	118 (70.7)
ANALGESIC	0	2 (1.2)
ANESTHETIC, GENERAL	1 (0.6)	1 (0.6)
ANESTHETIC, LOCAL	1 (0.6)	1 (0.6)
ANTICHOLINERGIC	25 (15.1)	31 (18.6)
ANTIDEPRESSANT	2 (1.2)	2 (1.2)
ANTIEPILEPTIC	19 (11.4)	21 (12.6)
ANTIMIGRAINE PREP	2 (1.2)	0
ANTIPSYCHOTIC	2 (1.2)	2 (1.2)
ANTIVERTIGO PREP	1 (0.6)	0
ANXIOLYTIC	73 (44.0)	79 (47.3)
HYPNOTIC & SEDATIVE	19 (11.4)	14 (8.4)
OPIOID	13 (7.8)	8 (4.8)
OTHER ANALGESIC & ANTIPYRETIC	49 (29.5)	38 (22.8)
OTHER NERVOUS SYSTEM DRUG	0	1 (0.6)
PSYCHOLEPTIC	1 (0.6)	1 (0.6)
PSYCHOSTIMULANT	1 (0.6)	0

Reviewer's Comments: I agree with the sponsor's assessment that the protocol violations and use of concomitant study medications are unlikely to have affected the results of the study. The use of EPS medications was similar in patients receiving placebo and aripiprazole.

Analysis of Primary Endpoint(s)

The primary efficacy measure was the time from randomization to relapse to any mood Episode. Patients in the placebo group relapsed sooner than patients in the aripiprazole group. The treatment difference between placebo and aripiprazole in the primary efficacy measure was statistically significant, favoring aripiprazole (p = 0.014). The proportion of relapses observed during the double-blind treatment period was 14.9% (25/168) in the aripiprazole group and 25.4% (43/169) in the placebo group. For those treated with lithium, patients in the placebo group relapsed sooner than patients in the aripiprazole group (p = 0.002); however, for those treated with valproate, no statistically significant difference was observed between aripiprazole and placebo treatment groups.

Table 8: Sponsor's Results for Primary Efficacy Variable

Variable	Placebo	Aripiprazole
Primary Efficacy Endpoint		
Time from randomization to relapse to any mood episode (overall)[a]		
No. Events/No. Patients (%)	43/169 (25.4)	25/168 (14.9)
Hazard Ratio		0.54
(95% CI)		(0.33, 0.89)
p-value		0.014

Table 9: Summary of Efficacy for Time to Event Analyses, Randomized Sample

Measurement Mood Stabilizer	Placebo Number of Events / Number of Patients (%)	Aripiprazole Number of Events / Number of Patients (%)	Treatment Comparison (a) Aripiprazole/Placebo Hazard Ratio	(95% CI)	p-value
Primary Efficacy Endpoint: Time from Randomization to Relapse to Any Mood Episode					
Overall	43/ 169 (25.4)	25/ 168 (14.9)	0.54	(0.33,0.89)	0.014
Lithium	26/ 66 (39.4)	10/ 70 (14.3)	0.33	(0.16,0.68)	0.002
Valproate	17/ 103 (16.5)	15/ 98 (15.3)	0.92	(0.46,1.85)	0.824
Other Efficacy Endpoint: Time from Randomization to Relapse of Manic Episode					
Overall	19/ 169 (11.2)	7/ 168 (4.2)	0.35	(0.15,0.83)	0.013
Lithium	13/ 66 (19.7)	4/ 70 (5.7)	0.27	(0.09,0.84)	0.015
Valproate	6/ 103 (5.8)	3/ 98 (3.1)	0.53	(0.13,2.13)	0.365
Time from Randomization to Relapse of Depressive Episode					
Overall	18/ 169 (10.7)	14/ 168 (8.3)	0.73	(0.36,1.48)	0.384
Lithium	9/ 66 (13.6)	5/ 70 (7.1)	0.46	(0.15,1.37)	0.152
Valproate	9/ 103 (8.7)	9/ 98 (9.2)	1.05	(0.42,2.64)	0.922

Figure 1: Kaplan-Meir Curves for Relapse to Any Mood Episodes

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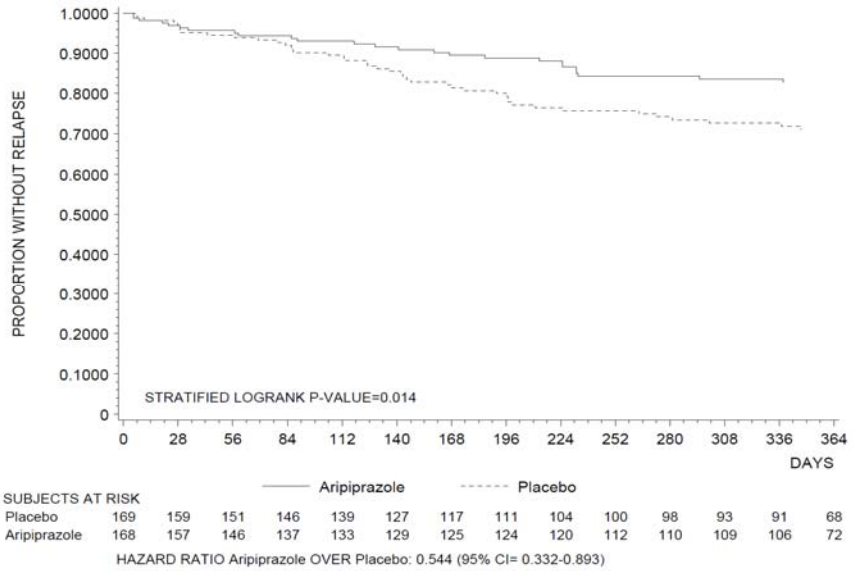

Key Secondary Endpoint

Key Secondary Endpoint

The key secondary efficacy measure was the mean change from baseline (end of Phase 2) to endpoint (Week 52 LOCF) in the CGI-BP Severity of Illness Score (mania). For this analysis, a hierarchical testing procedure was used so that the overall experiment-wise type I error rate was 0.05.

There was a statistically significant difference in favor of aripiprazole in the mean change from baseline in CGI-BP Severity of Illness Score (mania) at Week 52 (p = 0.013, LOCF) beginning at Week 24 and continuing through to endpoint. Results are statistically significant with the OC data set at Weeks 44 through 52.

Table 10: Sponsor's ANCOVA Results for Key Secondary Endpoint

Variable	Placebo	Aripiprazole
Key Secondary Endpoint		
CGI-BP Severity of Illness (Mania)[b]		
N	164	162
Mean baseline (SE)	1.54 (0.059)	1.54 (0.058)
Mean change Week 52 (SE)	0.32 (0.083)	0.04 (0.082)
Difference from Placebo		-0.28
(95% CI)		(-0.50, -0.06)
p-value		0.013

Other Endpoints

Type and Number of Relapses

Relapses were classified into 3 categories: manic type, depressive type, or mixed type. A relapse was classified as a manic type or depressive type if the patient met the

protocol-defined criteria for relapse and was discontinued with a mood status of manic symptoms or depressive symptoms, respectively. A relapse was classified as a mixed type if the patient met the protocol-defined criteria for relapse and was discontinued with a mood status of both manic and depressive symptoms.

Placebo-treated patients reported more relapses (25.4%) of any type mood episode than aripiprazole-treated patients (14.9%), and also when analyzed by patients receiving lithium (placebo 39.4%; aripiprazole 14.3%) and valproate (placebo 16.5%; aripiprazole 15.3%).

Table 11: Type of Relapses, Randomized Sample

	Number Relapsed (%)					
	Lithium		Valproate		Overall	
TYPE OF RELAPSE	Placebo N=66	Aripiprazole N=70	Placebo N=103	Aripiprazole N=98	Placebo N=169	Aripiprazole N=168
MANIC	13 (19.7)	4 (5.7)	6 (5.8)	3 (3.1)	19 (11.2)	7 (4.2)
DEPRESSIVE	9 (13.6)	5 (7.1)	9 (8.7)	9 (9.2)	18 (10.7)	14 (8.3)
MIXED	4 (6.1)	1 (1.4)	2 (1.9)	3 (3.1)	6 (3.6)	4 (2.4)
TOTAL	26 (39.4)	10 (14.3)	17 (16.5)	15 (15.3)	43 (25.4)	25 (14.9)

Mean Change from Baseline in Y-MRS Total Score

At Week 52, the treatment difference between the groups in the mean change from baseline in Y-MRS Total Score was statistically significant in favor of aripiprazole.

Table 12: Adjusted Mean Change from Baseline in Y-MRS Total Score, LOCF Data Set, Phase 3 Efficacy Sample.

		Placebo			Aripiprazole			Treatment Comparisons (b) Aripiprazole - Placebo		
	Visit	N	Mean (a)	(SE)	N	Mean (a)	(SE)	Difference	(95% CI)	p-value
Mean Baseline		164	4.03	(0.285)	162	4.06	(0.280)	0.02	(-0.73,0.77)	0.955
Mean Change from Baseline to	Week 4	160	0.47	(0.342)	162	0.53	(0.332)	0.06	(-0.83,0.95)	0.895
	Week 8	164	0.91	(0.353)	162	0.23	(0.346)	-0.69	(-1.61,0.24)	0.144
	Week 12	164	1.53	(0.415)	162	0.43	(0.408)	-1.10	(-2.19,-0.01)	0.047
	Week 16	164	1.74	(0.433)	162	0.35	(0.425)	-1.39	(-2.52,-0.25)	0.017
	Week 20	164	2.29	(0.472)	162	0.38	(0.463)	-1.91	(-3.15,-0.68)	0.003
	Week 24	164	2.42	(0.492)	162	0.24	(0.483)	-2.18	(-3.47,-0.89)	<0.001
	Week 28	164	3.02	(0.547)	162	0.40	(0.537)	-2.62	(-4.06,-1.19)	<0.001
	Week 32	164	2.72	(0.526)	162	0.39	(0.516)	-2.33	(-3.70,-0.95)	<0.001
	Week 36	164	3.04	(0.538)	162	0.26	(0.528)	-2.78	(-4.19,-1.37)	<0.001
	Week 40	164	2.82	(0.542)	162	0.11	(0.532)	-2.71	(-4.13,-1.29)	<0.001
	Week 44	164	3.19	(0.558)	162	0.27	(0.548)	-2.92	(-4.38,-1.46)	<0.001
	Week 48	164	3.15	(0.575)	162	0.07	(0.564)	-3.08	(-4.59,-1.57)	<0.001
	Week 52	164	2.93	(0.576)	162	-0.11	(0.565)	-3.04	(-4.55,-1.54)	<0.001

Mean Change from Baseline in MADRS Total Score

There was a statistically significant difference between treatment groups in favor of aripiprazole in the adjusted mean change from baseline in the MADRS Total Score at Week 52.

Table 13: Adjusted mean Change from Baseline in MADRS Total Score, LOCF Data Set, Phase 3 Efficacy Sample

		Placebo			Aripiprazole			Treatment Comparisons (b) Aripiprazole - Placebo		
	Visit	N	Mean (a)	(SE)	N	Mean (a)	(SE)	Difference	(95% CI)	p-value
Mean Baseline		164	4.41	(0.282)	162	4.62	(0.277)	0.20	(-0.54,0.94)	0.590
Mean Change from Baseline to	Week 4	160	1.92	(0.421)	162	1.42	(0.411)	-0.50	(-1.59,0.60)	0.371
	Week 8	164	2.27	(0.495)	162	1.23	(0.488)	-1.04	(-2.33,0.25)	0.113
	Week 12	164	2.42	(0.493)	162	1.42	(0.486)	-1.00	(-2.28,0.29)	0.128
	Week 16	164	2.12	(0.505)	162	1.27	(0.498)	-0.85	(-2.16,0.47)	0.205
	Week 20	164	2.61	(0.557)	162	1.47	(0.549)	-1.13	(-2.59,0.32)	0.125
	Week 24	164	2.92	(0.572)	162	1.49	(0.564)	-1.43	(-2.92,0.06)	0.061
	Week 28	164	3.14	(0.601)	162	1.64	(0.594)	-1.51	(-3.07,0.06)	0.060
	Week 32	164	3.32	(0.609)	162	1.70	(0.601)	-1.62	(-3.21,-0.03)	0.046
	Week 36	164	3.03	(0.621)	162	1.89	(0.612)	-1.15	(-2.77,0.47)	0.164
	Week 40	164	3.18	(0.626)	162	1.65	(0.618)	-1.53	(-3.16,0.10)	0.066
	Week 44	164	3.10	(0.641)	162	1.53	(0.632)	-1.57	(-3.24,0.10)	0.066
	Week 48	164	3.57	(0.633)	162	1.48	(0.624)	-2.08	(-3.73,-0.43)	0.014
	Week 52	164	3.47	(0.640)	162	1.46	(0.632)	-2.01	(-3.68,-0.34)	0.019

Mean Change from Baseline in CGI-BP Severity of Illness Score (Depression)

The adjusted mean change from baseline to Week 52 (LOCF) in the CGI-BP Severity of Illness Score (depression) was not statistically significant.

Mean Change from Baseline in CGI-BP Severity of Illness Score (Overall)

The adjusted mean change from baseline in the CGI-BP Severity of Illness Score (overall) was statistically significant in favor of aripiprazole at Week 52 (LOCF) beginning at Week 24 in the Phase 3 Efficacy Sample.

Table 14: Adjusted mean Change from baseline in CGI-BP Severity of Illness (Overall) Score, LOCF Data set, Phase 3 Efficacy Sample.

		Placebo			Aripiprazole			Treatment Comparisons (b) Aripiprazole - Placebo		
	Visit	N	Mean (a)	(SE)	N	Mean (a)	(SE)	Difference	(95% CI)	p-value
Mean Baseline		164	1.65	(0.065)	162	1.70	(0.064)	0.05	(-0.13,0.22)	0.597
Mean Change from Baseline to	Week 4	160	0.25	(0.072)	162	0.27	(0.070)	0.02	(-0.17,0.21)	0.838
	Week 8	164	0.32	(0.080)	162	0.21	(0.079)	-0.11	(-0.32,0.10)	0.291
	Week 12	164	0.40	(0.087)	162	0.26	(0.085)	-0.14	(-0.37,0.08)	0.219
	Week 16	164	0.44	(0.088)	162	0.26	(0.087)	-0.18	(-0.41,0.05)	0.133
	Week 20	164	0.51	(0.095)	162	0.29	(0.094)	-0.21	(-0.46,0.04)	0.092
	Week 24	164	0.56	(0.097)	162	0.25	(0.095)	-0.31	(-0.56,-0.05)	0.018
	Week 28	164	0.62	(0.101)	162	0.32	(0.099)	-0.29	(-0.56,-0.03)	0.029
	Week 32	164	0.61	(0.102)	162	0.30	(0.100)	-0.31	(-0.57,-0.04)	0.024
	Week 36	164	0.62	(0.103)	162	0.33	(0.101)	-0.29	(-0.56,-0.02)	0.035
	Week 40	164	0.57	(0.104)	162	0.28	(0.102)	-0.29	(-0.56,-0.02)	0.038
	Week 44	164	0.64	(0.105)	162	0.30	(0.103)	-0.34	(-0.62,-0.07)	0.015
	Week 48	164	0.68	(0.106)	162	0.28	(0.104)	-0.39	(-0.67,-0.12)	0.006
	Week 52	164	0.66	(0.106)	162	0.31	(0.104)	-0.35	(-0.62,-0.07)	0.015

Mean CGI-BP Change from Preceding Phase Score (Mania)

There was a statistically significant difference between treatment groups in favor of aripiprazole in the adjusted mean CGI-BP change from preceding phase score (mania) at Weeks 28 and 36 through 52.

Table 15: Adjusted mean Change from Preceding Phase (Mania) Score, LOCF Data Set, Phase 3 Sample

	Placebo			Aripiprazole			Treatment Comparisons (b) Aripiprazole - Placebo		
Visit	N	Mean (a)	(SE)	N	Mean (a)	(SE)	Difference	(95% CI)	p-value
Week 4	160	2.96	(0.111)	162	3.00	(0.108)	0.04	(-0.25,0.33)	0.774
Week 8	164	3.17	(0.113)	162	2.98	(0.111)	-0.19	(-0.49,0.11)	0.213
Week 12	164	3.14	(0.118)	162	3.03	(0.116)	-0.12	(-0.43,0.20)	0.465
Week 16	164	3.27	(0.118)	162	2.98	(0.115)	-0.29	(-0.59,0.02)	0.068
Week 20	164	3.29	(0.120)	162	3.03	(0.118)	-0.27	(-0.58,0.05)	0.095
Week 24	164	3.26	(0.125)	162	2.96	(0.123)	-0.29	(-0.62,0.04)	0.082
Week 28	164	3.37	(0.126)	162	3.01	(0.124)	-0.36	(-0.69,-0.03)	0.033
Week 32	164	3.31	(0.124)	162	3.00	(0.122)	-0.31	(-0.64,0.02)	0.062
Week 36	164	3.37	(0.125)	162	2.94	(0.123)	-0.43	(-0.76,-0.10)	0.011
Week 40	164	3.32	(0.126)	162	2.94	(0.124)	-0.37	(-0.70,-0.04)	0.027
Week 44	164	3.33	(0.128)	162	2.96	(0.125)	-0.37	(-0.71,-0.04)	0.029
Week 48	164	3.35	(0.130)	162	2.96	(0.128)	-0.40	(-0.74,-0.06)	0.022
Week 52	164	3.29	(0.131)	162	2.89	(0.129)	-0.40	(-0.75,-0.06)	0.023

Mean CGI-BP Change from Preceding Phase Score (Depression)

There was no statistically significant difference between treatment groups in the adjusted mean CGI-BP change from preceding phase score (depression) at any week (LOCF).

Mean CGI-BP Change from Preceding Phase Score (Overall)

There was no statistically significant difference between treatment groups in the adjusted mean CGI-BP change from preceding phase score (overall) at Week 52 (LOCF).

Maintenance of Remission

Patients with a Y-MRS Total Score and MADRS Total Score ≤ 12 were considered remitters for that given visit. There was no statistically significant difference between treatment groups in remission rates reported at endpoint (Week 52) in the OC data set, Phase 3 Efficacy Sample.

Time from Randomization to Relapse of Manic Episode

More placebo-treated than aripiprazole-treated patients experienced the relapse of a

manic episode during Phase 3. A statistically significant difference between the groups was observed for time from randomization to relapse during Phase 3,

Time from Randomization to Relapse of Depressive Episode

There was no statistically significant difference between treatment groups reported for time from randomization to relapse of depressive episode during Phase 3,

Time from Randomization to Discontinuation for Any Reason

There was no statistically significant difference between treatment groups reported for time from randomization to discontinuation for any reason during Phase 3.

Crosscutting Issues

Subpopulations

Gender: A total of 152 (45.1%) randomized patients were males. The proportions of observed relapses were similar between males (26.8%) and females (24.5%) in the placebo group, while males in the aripiprazole group (9.9%) appeared to have a lower proportion of observed relapses than females (19.5%). Moreover, the treatment difference in the primary efficacy endpoint seemed to be greater in males than in females.

Race: A total of 230 (68.2%) randomized patients were white. A numerically smaller proportion of responses was observed in non-whites (placebo: 21.1%; aripiprazole: 10.0%) than in whites (placebo: 27.7%; aripiprazole: 16.9%) in each treatment group. Those proportions in non-whites were uncertain due to insufficient sample size.

Age: Patient's age at date of informed consent ranged from 18 to 74 in the Randomized Sample. The average and median age was 39.

Type of Mood Stabilizer: There were 136 (40.4%) randomized patients who had lithium as their mood stabilizer. The log-rank test stratified by type of index mood episode reached nominal significance for the lithium subgroup (p = 0.002), but not for the valproate subgroup (p = 0.824). The sponsor remarked that those results were inconsistent with the results in a previous aripiprazole study (CN138134), where nominal significance was seen in the valproate subgroup, but not in the lithium subgroup.

Type of Index Mood Episode: A total of 230 (68.2%) randomized patients displayed a manic mood episode upon study entry. The log-rank test stratified by type of mood stabilizer reached nominal significance for the manic episode subgroup (p = 0.004), but not for the mixed episode subgroup (p = 0.951).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

None

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

None

6.1.10 Additional Efficacy Issues/Analyses

None

Conclusions

The sponsor has conducted one randomized, double-blind, placebo-controlled adjunctive-therapy, long term study and has demonstrated that treatment with aripiprazole in combination with lithium or valproate is efficacious in the long term treatment of patients with bipolar I disorder, who are partially nonresponsive to mood stabilizer monotherapy. The statistical reviewer confirmed the sponsor's primary finding that the time to relapse of any mood episode observed in Phase 3 was statistically

significantly delayed in the aripiprazole group, as compared to the placebo group. However, the statistical reviewer had the following comments:

Key Secondary Endpoint: The sponsor designated "change from baseline to Week 52 in CGI-BP Severity of Illness (mania) score" as a key secondary endpoint. Although the sponsor's primary results for this "key" secondary efficacy endpoint were statistically significant (p = 0.013; Phase 3 Efficacy Sample), they should not be described in the Clinical Studies Section. This is because that it is questionable to use CGI-BP severity of illness (mania) score as a key secondary endpoint in such a maintenance study due to potentially informative dropouts, particularly when the dropout rate is expected to be large.

Large Proportion of Randomized Patients with Protocol Deviations: There were a total of 133 (39.5%) randomized patients with protocol deviations relating to the inclusion/exclusion criteria, study conduct, patient management, or patient assessments. The primary stratified log-rank test on the Phase 3 Per-protocol Sample failed to reach nominal significance (p = 0.060), but this may be due to insufficient sample size.

Relapse of Mood Episode of a Specific Type: The primary efficacy endpoint (time to relapse of any mood episode) was a composite endpoint, defined as time to a manic, mixed, or depressive mood episode observed in Phase 3. A smaller proportion of relapses were observed in the aripiprazole group (25/168; 14.9%) than in the placebo group (43/169; 25.4%) in Phase 3, favoring aripiprazole. However, it was inappropriate to use Kaplan-Maier (KM) method to estimate the time to relapse by type of mood episode (manic or depressive) for this study. The information conveyed by the sponsor's KM curves was unreliable due to the small number of mood episodes of a specific type (manic: 26; depressive: 32) observed in Phase 3. In addition, since the 68 randomized patients who discontinued the study after relapse of a mood episode were

not followed up till the end of Phase 3, their relapses of the first mood episode of other types that occurred within 52 weeks after randomization were not counted in the KM estimation. Therefore, it was uncertain whether aripiprazole was effective in delaying the time to relapse of manic (or depressive) mood episode in this study.

Treatment Effects among Subgroups: In this study, treatment difference (aripiprazole vs. placebo) appeared to be greater in males than in females, in lithium subgroup than in valproate subgroup, and in patients with manic index mood episode than in patients with mixed index mood episode, as assessed by both the primary and the key secondary endpoints. The treatment different in the primary efficacy endpoint seemed to greater in non-US patients than US patients; while on the contrary, the treatment difference in the key secondary endpoint seemed to be greater in US patients than in non-US patients.

7 Review of Safety

Safety Summary

Overall, the safety and tolerability from Study CN138189 have been consistent with previous clinical studies involving ABILIFY and no new safety signals were detected.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There was only one study used to evaluate safety.

CN138189: Efficacy of Aripiprazole in Combination with Lithium or Valproate in the Long Term Treatment of Mania in Patients with Bipolar I Disorder Partially Nonresponsive to Lithium or Valproate Monotherapy

7.1.2 Categorization of Adverse Events

An AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition regardless of causal relationship with treatment.

A SAE was any untoward medical occurrence at any dose that:

- resulted in death
- was life-threatening (defined as an event in which the patient or patient was at risk of death at the time of the event; it did not refer to an event which hypothetically might have caused death if it were more severe)
- required inpatient hospitalization or caused prolongation of existing hospitalization
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect
- resulted in the development of drug dependency or drug abuse
- was an important medical event (including pregnancy, cancer, or overdose)

When it was discovered that a trial patient was pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product was permanently discontinued in an appropriate manner.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable as there was only one study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For Phase 3, 337 patients of the 346 who completed Phase 2 were randomized. At 52 weeks (364 days) of double-blind treatment, approximately 89 (52.4%) patients receiving placebo and 103 (61.3%) patients receiving aripiprazole completed the study.

The mean aripiprazole dose at 364 days was 16.3 mg/day. The mean aripiprazole dose ranged from 15.8 to 16.9 mg/day throughout the entire double-blind treatment phase. When analyzed by mood stabilizer subgroups, the mean aripiprazole dose at 364 days of aripiprazole treatment was 14.6 mg/day in patients receiving lithium and 17.6 mg/day in patients receiving valproate.

Of the 337 randomized patients, all but 4 patients were included in the Safety Sample:

Placebo Group:
• 1 patient was lost to follow up (CN138189-5-322)
• 1 patient withdrew consent (CN138189-64-767)
• 1 patient no longer met study criteria (CN138189-90-470)

Aripiprazole Group:
• 1 patient withdrew consent to participate (CN138189-123-916).

Reviewer's Comments: I am of the opinion that the sponsor has studied an adequate number of subjects for an adequate period of time as recommended in the ICH guidelines, i.e. 100 patients for one year.

7.2.2 Explorations for Dose Response

No explorations for dose response were conducted.

7.2.3 Special Animal and/or In Vitro Testing

None done

7.2.4 Routine Clinical Testing

Routine clinical testing included monitoring the frequency and severity of AEs, serious adverse events (SAEs) (clinical and laboratory) and discontinuations from study due to AEs, vital signs (supine and standing positions), body weight, electrocardiogram (ECG), routine and special laboratory tests (including CPK and homeostasis model assessment

of insulin resistance [HOMA-IR]), and physical examination. Safety and tolerability of study medication was evaluated by reports of AEs including potentially clinically significant changes in ECGs, vital signs, physical examinations, and clinical laboratory tests. Safety and tolerability of study medication was also evaluated by the change from baseline in movement disorder scale scores (Simpson-Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes-Akathisia Global Clinical Rating Scale).

7.2.5 Metabolic, Clearance, and Interaction Workup

None

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Major concerns with drugs in this class include the risk of extrapyramidal adverse events and metabolic syndrome. The sponsor has adequately monitored these adverse events and they are described in more detail in the review.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during Phases 1 and 2 of the study. There were two deaths reported during Phase 3.

A 57 year old lady with a history of breast cancer since December 2005 entered the study in stable phase. She had undergone a right mastectomy, chemotherapy and radiotherapy in 2006. She was assigned to valproate. On Day 388, (b) (6) at a total daily dose of valproate 250 mg and 10 mg of aripiprazole, the subject was hospitalized due to progression of the breast cancer with bone metastases and medular

compression. The study medications were discontinued. On day 403 (b) (6) the subject experienced cardiorespiratory arrest and died.

A 51- year old male was assigned to lithium in phase 1. He entered the single-blind Phase 2 on lithium 600 mg and received aripiprazole 15 mg. He was randomized to the double blind phase and assigned to continued treatment with aripiprazole. On day 195, at a total daily dose of 15 mg aripiprazole and 900 mg lithium, the subject died due to decapitation caused by a train accident. There was no suicide note found at the accident. There were no other significant injuries noted. There was no history of suicidality in the past. At the last visit prior to the event, the subject had a MADRS score of 7 and the YMRS score was 0.

Reviewer's Comments: I reviewed the narratives of both the events in detail. It is possible that the male who died by decapitation was a suicide. However, suicide is not uncommon in patients with bipolar disorder, and I do not think that it is related to study drug in this instance. I am convinced that both the events were not related to the study drug.

Nonfatal Serious Adverse Events

Phase 3 (Double-blind Phase)

Nineteen patients reported 21 treatment emergent serious adverse events (SAE's) during Phase 3: Placebo, 8 (4.8%) & aripprazole, 11 (6.6%). The most common SAE's reported in placebo-treated patients were mania, depression, and cellulitis (each 1.2%); for aripiprazole treated patients, the most common SAE's were mania and bartholin's cyst (each 1.2%). All other SAE's were reported once.

Table 16: Incidence of Treatment-Emergent serious Adverse Events during Phase 3

SYSTEM ORGAN CLASS PREFERRED TERM	Incidence (%) Placebo	 Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	166	167
NUMBER OF MALE PATIENTS	70	81
NUMBER OF FEMALE PATIENTS	96	86
ANY SERIOUS ADVERSE EVENT	8 (4.8)	11 (6.6)
PSYCHIATRIC DISORDERS	5 (3.0)	7 (4.2)
MANIA	2 (1.2)	2 (1.2)
AGGRESSION	0	1 (0.6)
AGITATION	0	1 (0.6)
BIPOLAR DISORDER	0	1 (0.6)
DEPRESSION	2 (1.2)	1 (0.6)
SUICIDAL IDEATION	0	1 (0.6)
SUICIDE ATTEMPT	0	1 (0.6)
BIPOLAR I DISORDER	1 (0.6)	0
INFECTIONS AND INFESTATIONS	2 (1.2)	2 (1.2)
APPENDICITIS	0	1 (0.6)
CELLULITIS	2 (1.2)	1 (0.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (0.6)
DECAPITATION	0	1 (0.6)
RENAL AND URINARY DISORDERS	0	1 (0.6)
RENAL FAILURE ACUTE	0	1 (0.6)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	1 (0.6)
BARTHOLIN'S CYST (F)	0	1 (1.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.6)	0
BREAST CANCER	1 (0.6)	0

In Phase 2 of the study, 15 (2.2%) patients reported an SAE. More patients on valproate 10 (2.6%) reported a SAE than in the lithium group 5 (1.7%). The most common SAE reported were Psychiatric SAE's, including depression, psychosis and suicide attempt. There was also one case of chest pain and one of non-cardiac chest pain. There was one case of accidental overdose in the lithium and valproate group. One subject in the valproate group had a leiomyoma and one had a radial nerve palsy.

Reviewer's Comments: I reviewed the narratives of all SAE's. Most of the SAE's reported were psychiatric disorders, which are part of the disease process.

7.3.3 Dropouts and/or Discontinuations

There were 34 patients with at least 1 treatment-emergent AE reported during Phase 3 (Safety Sample) that led to discontinuation of study therapy: 15 (9.0%) in the placebo group and 19 (11.4%) in the aripiprazole group. Most of the AEs resulting in discontinuation were psychiatric disorders. The most common AEs leading to discontinuation of study therapy for placebo-treated patients were mania (3.0%), depressive symptoms (2.4%), and depression (1.8%).

The most common AEs leading to discontinuation of study therapy for aripiprazole - treated patients were depression (4.2%), mania (2.4%), and depressive symptoms (1.8%).

Two patients discontinued from the study due to laboratory-related AE's: Patient CN138189-68-287 (aripiprazole/valproate) with moderate hyperprolactinemia during Phase 3, Patient CN138189-90-567 (single-blind aripiprazole/valproate) with moderate increased ALT and severe increased AST (137U/L) during Phase 2.

Seven patients reported suicide-related events (suicide attempt/suicidal ideation) that resulted in discontinuation from study therapy: 4 patients in Phase 1, 1 patient in Phase 2, and 2 patients in Phase 3 of the study.

In Phase 3, Patient CN138189-25-151, a 32-year-old white female receiving valproate 750 mg and aripiprazole 30 mg, reported a very severe suicide attempt by overdose. The patient was discontinued from study drug on Phase 3 Day 158.

In Phase 3, Patient CN138189-115-1244, a 50-year-old white female receiving lithium 750 mg and aripiprazole 10 mg, reported moderate suicidal ideation with an onset on Phase 3. The patient was discontinued from study drug as a result of this event.
In addition, there was a death due to decapitation secondary to being hit by a train, judged by the investigator to be a completed suicide and not related to study drug.

Table 17: Events Leading to Discontinuiation

SYSTEM ORGAN CLASS PREFERRED TERM	Incidence (%) Placebo	 Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	166	167
NUMBER OF MALE PATIENTS	70	81
NUMBER OF FEMALE PATIENTS	96	86
ANY ADVERSE EVENT LEADING TO DISCONTINUATION	15 (9.0)	19 (11.4)
PSYCHIATRIC DISORDERS	14 (8.4)	17 (10.2)
DEPRESSION	3 (1.8)	7 (4.2)
MANIA	5 (3.0)	4 (2.4)
DEPRESSIVE SYMPTOM	4 (2.4)	3 (1.8)
AGGRESSION	0	1 (0.6)
AGITATION	0	1 (0.6)
SUICIDAL IDEATION	0	1 (0.6)
SUICIDE ATTEMPT	0	1 (0.6)
BIPOLAR I DISORDER	1 (0.6)	0
MOOD ALTERED	1 (0.6)	0
CARDIAC DISORDERS	0	1 (0.6)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	0	1 (0.6)
ENDOCRINE DISORDERS	0	1 (0.6)
HYPERPROLACTINAEMIA	0	1 (0.6)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.6)	0
BREAST CANCER	1 (0.6)	0

In Phase 2 (Open Label Phase), there were 38 (13%) discontinuiations in the lithium group and 50 (12.8%) in the valproate group. The majority of discontinuiations were for psychiatric disorders, 17 (5.8%) in the lithium group and 22 (5.6%) in the valproate group. Nervous system disorders accounted for the next most number of discontinuiations, 18 (6.2%) in the lithium group and 23 (5.9%) in the valproate group.

Reviewer's Comments: I reviewed the Case report Forms (CRF) of Patient CN138189-25-151. The patient took an overdose of 5250 mg of depakote and 60 mg of abilify/placebo. This was an impulsive overdose with an intent to kill herself. Subject was admitted to the hospital but no medical treatment was performed. The subject was discharged after 6 days.
CRF of Patient CN138189-115-1244, had suicidal ideation with no suicide attempt, but was hospitalized and discontinued from the study.

The sponsor also coded separately for depression and depressive symptoms. I am of the opinion that they represent the same AE and hence should have been coded under depression. However, combining both does not significantly alter the safety conclusions of the study.

7.3.4 Significant Adverse Events

There were no other significant adverse events reported.

7.3.5 Submission Specific Primary Safety Concerns

Extrapyramidal syndrome-related adverse events are of significant concern with drugs in the antipsychotic class. There were 26 patients with at least 1 treatment-emergent EPS related AE reported during Phase 3: placebo 7 (4.2%); aripiprazole 19 (11.4%).

The most frequent EPS-related AEs were:

Placebo: tremor (2.4%) and akathisia (1.8%)

Aripiprazole: tremor (6%), akathisia (3.6%), and extrapyramidal disorder (3%).

Table 18: Incidence of Treatment-Emergent EPS-Related Adverse Events during Phase-3

EPS CATEGORY PREFERRED TERM	Incidence (%) Placebo	 Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	166	167
NUMBER OF MALE PATIENTS	70	81
NUMBER OF FEMALE PATIENTS	96	86
ANY EPS-RELATED ADVERSE EVENT	7 (4.2)	19 (11.4)
PARKINSONISM EVENTS	5 (3.0)	14 (8.4)
TREMOR	4 (2.4)	10 (6.0)
EXTRAPYRAMIDAL DISORDER	1 (0.6)	5 (3.0)
PARKINSONISM	0	1 (0.6)
AKATHISIA EVENTS	3 (1.8)	6 (3.6)
AKATHISIA	3 (1.8)	6 (3.6)
DYSTONIC EVENTS	0	2 (1.2)
MUSCLE RIGIDITY	0	1 (0.6)
MUSCLE SPASMS	0	1 (0.6)
DYSKINETIC EVENTS	2 (1.2)	0
DYSKINESIA	1 (0.6)	0
TARDIVE DYSKINESIA	1 (0.6)	0

In the Phase 2 (open-label phase), 108 (37% of patients on lithium and 113 (29%) of patients on valproate experienced an EPS related adverse event. Parkinsonian events were seen in 62 (21.2%) of subjects on lithium and 72 (18.5%) of subjects on valproate. Akathisia was seen in 50 (17%) of subjects on lithium and 50 (12.8%) of subjects on valproate.

Reviewer's Comments: Extrapyramidal AE's including tremors and akathisia are described in the current label of aripiprazole. They have been observed at almost three times the rates seen in placebo. In combination therapy with lithium or valproate, they do not seem to be present at increased frequency compared to rates seen in monotherapy trials (approximately 10%). However, the rates of akathisia seem to be seen with greater frequency in Phase 2 (14.5% compared to 6% in Phase 3). This is not unusual as akathisia commonly is seen early on in treatment. It is also reassuring to note that there were no increased rates of tardive dyskinesia with aripiprazole compared to placebo in this study.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The incidences of AE's that occurred in >2% of patients in any treatment group during Phase 3 show that twenty-nine (29.5%) placebo treated patients reported at least 1 treatment-related AE and 62 (37.1%) aripiprazole treated patients reported at least 1 treatment-related AE. The most frequently reported AEs were:

- Placebo: weight increased (4.8%), headache (3.6%), insomnia and mania (each 3.0%), and tremor (2.4%)
- Aripiprazole: weight increased (7.2%), headache and tremor (each 5.4%), akathisia (3.6%), extrapyramidal disorder (3.0%), and dizziness and diarrhea (each 2.4%).

During Phase 3 (Safety Sample), the treatment-emergent AEs with a ≥ 2% difference in the aripiprazole group (placebo subtracted from aripiprazole) were tremor (3.6%), extrapyramidal disorder, dizziness, weight increased, vomiting, and depression (each 2.4%), and headache (2.3%).

Table 19: Incidence of Treatment-Related Adverse Events That Occurred in Greater Than or Equal To 2 Percent of Patients in Any Treatment Group During Phase 3, Phase 3 Safety Sample

SYSTEM ORGAN CLASS PREFERRED TERM	Incidence (%) Placebo	 Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	166	167
NUMBER OF MALE PATIENTS	70	81
NUMBER OF FEMALE PATIENTS	96	86
ANY TREATMENT-RELATED ADVERSE EVENT	49 (29.5)	62 (37.1)
NERVOUS SYSTEM DISORDERS	18 (10.8)	31 (18.6)
HEADACHE	6 (3.6)	9 (5.4)
TREMOR	4 (2.4)	9 (5.4)
AKATHISIA	3 (1.8)	6 (3.6)
EXTRAPYRAMIDAL DISORDER	1 (0.6)	5 (3.0)
DIZZINESS	1 (0.6)	4 (2.4)
INVESTIGATIONS	8 (4.8)	14 (8.4)
WEIGHT INCREASED	8 (4.8)	12 (7.2)
GASTROINTESTINAL DISORDERS	7 (4.2)	10 (6.0)
DIARRHOEA	2 (1.2)	4 (2.4)
PSYCHIATRIC DISORDERS	15 (9.0)	8 (4.8)
INSOMNIA	5 (3.0)	2 (1.2)
MANIA	5 (3.0)	2 (1.2)

Table 20: Incidence of Treatment-Emergent Adverse Events That Occurred in Greater Than or Equal To 5 Percent of Patients in Any Treatment Group During Phase 3, Phase 3 Safety Sample

SYSTEM ORGAN CLASS PREFERRED TERM	Incidence (%) Placebo	 Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	166	167
NUMBER OF MALE PATIENTS	70	81
NUMBER OF FEMALE PATIENTS	96	86
ANY ADVERSE EVENT	105 (63.3)	105 (62.9)
NERVOUS SYSTEM DISORDERS	34 (20.5)	44 (26.3)
HEADACHE	18 (10.8)	22 (13.2)
TREMOR	4 (2.4)	10 (6.0)
PSYCHIATRIC DISORDERS	37 (22.3)	33 (19.8)
INSOMNIA	16 (9.6)	9 (5.4)
INVESTIGATIONS	18 (10.8)	21 (12.6)
WEIGHT INCREASED	11 (6.6)	15 (9.0)

7.4.2 Laboratory Findings

A central laboratory designated by BMS was used for all laboratory testing whenever possible (including unscheduled and follow-up labs if needed) and for all laboratory testing required during the study.

Urine was collected and fasting blood was drawn from each patient at the screening visit and at Weeks 4 and 8/End of Phase 1 during Phase 1; at Weeks 4, 8, 12, 16, 20 and 24/End of Phase visit during Phase 2; and at Weeks 4, 8, 12, 24, 36, and 52/early termination visit during Phase 3. Lithium and valproate serum levels were measured. A total of 2 patients discontinued from the study due to laboratory-related AE's. One patient (aripiprazole/valproate) had moderate hyperprolactinemia during Phase 3 and one (single-blind aripiprazole/valproate) with moderate increased ALT and severe AST during Phase 2.

Abnormal metabolic parameters were based on the following criteria from the National Cholesterol Education Program (NCEP):

- Fasting serum glucose ≥ 100 mg/dL
- LDL cholesterol (both fasting and nonfasting values) ≥100 mg/dL
- HDL cholesterol (both fasting and nonfasting values) < 40 mg/dL for men; < 50 mg/dL for women
- Fasting total triglycerides ≥ 150 mg/dL
- Total cholesterol (both fasting and nonfasting values) ≥ 200 mg/dL

In general, the incidence of abnormal metabolic parameters was similar between treatment groups, except with non-fasting HDL cholesterol values (placebo: 71.1%, aripiprazole 51.9%).

Table 21: Number of Patients with Metabolic Laboratory Parameters Abnormalities During Phase 3.

LAB MEASUREMENT	INCIDENCE (%)	
	Placebo	Aripiprazole
NUMBER OF PATIENTS IN SAFETY SAMPLE	166	167
METABOLIC		
Glucose (fast.) (mg/dL)	77/ 159 (48.4)	79/ 158 (50.0)
HDL Cholesterol (fast.) (mg/dL)	101/ 160 (63.1)	115/ 159 (72.3)
HDL Cholesterol (non-fast.) (mg/dL)	27/ 38 (71.1)	14/ 27 (51.9)
Cholesterol, Total (fast.) (mg/dL)	73/ 160 (45.6)	84/ 159 (52.8)
Cholesterol, Total (non-fast.) (mg/dL)	13/ 38 (34.2)	9/ 27 (33.3)
LDL Cholesterol (fast.) (mg/dL)	121/ 160 (75.6)	120/ 159 (75.5)
LDL Cholestrol (non-fast.) (mg/dL)	19/ 38 (50.0)	18/ 27 (66.7)
Triglycerides (fast.) (mg/dL)	91/ 160 (56.9)	100/ 159 (62.9)

Table 22: Number of Patients with Metabolic Laboratory Abnormalities During Phase 2

LAB MEASUREMENT	INCIDENCE (%)		
	Lithium	Valproate	Overall
NUMBER OF PATIENTS IN SAFETY SAMPLE	292	390	682
METABOLIC			
Glucose (fast.) (mg/dL)	128/ 251 (51.0)	123/ 332 (37.0)	251/ 583 (43.1)
HDL Cholesterol (fast.) (mg/dL)	138/ 252 (54.8)	183/ 332 (55.1)	321/ 584 (55.0)
HDL Cholesterol (non-fast.) (mg/dL)	38/ 79 (48.1)	44/ 91 (48.4)	82/ 170 (48.2)
Cholesterol, Total (fast.) (mg/dL)	104/ 252 (41.3)	132/ 332 (39.8)	236/ 584 (40.4)
Cholesterol, Total (non-fast.) (mg/dL)	23/ 79 (29.1)	32/ 92 (34.8)	55/ 171 (32.2)
LDL Cholesterol (fast.) (mg/dL)	169/ 252 (67.1)	223/ 332 (67.2)	392/ 584 (67.1)
LDL Cholestrol (non-fast.) (mg/dL)	41/ 79 (51.9)	52/ 91 (57.1)	93/ 170 (54.7)
Triglycerides (fast.) (mg/dL)	124/ 252 (49.2)	162/ 332 (48.8)	286/ 584 (49.0)

The most frequently reported potentially relevant abnormality was increased prolactin which occurred in 8.6% of placebo treated patients and 8.9% of aripiprazole treated patients, with mean values in placebo-treated patients increasing and mean values in aripiprazole treated patients decreasing from baseline.

Table 23: Mean Change from Baseline in Serum Prolactin, Phase 3 safety sample.

	Adjusted Mean Changes from Baseline (Mean Actual Score for Baseline) (a)					
	Placebo			Aripiprazole		
Visit	N	Mean	SE	N	Mean	SE
Baseline	154	9.90	1.05	147	8.62	1.07
Week 12	122	1.39	0.61	121	-0.39	0.61
Week 24	107	1.40	0.93	112	0.31	0.90
Week 36	87	1.64	1.00	91	-0.29	0.96
Week 52	79	0.28	0.97	88	-0.85	0.89
Week 52 (LOCF)	154	1.50	0.65	147	-0.51	0.67
Highest Value	154	4.45	0.84	147	2.52	0.85
Week 52 (LOCF)						
Treatment Difference, 95% CI					-2.01 (-3.83,-0.18)	
p-value					0.031	
Highest Value						
Treatment Difference, 95% CI					-1.93 (-4.27,0.41)	
p-value					0.105	

Change of prolactin level from baseline to week 52 was significant in patients who were on lithium -2.84 (95% CI -5.14, -0.54), while not for patients who were on valproate -1.40 (95% CI -3.87, 1.08).

Table 24: Number of patients with Potentially Clinically Relevant Laboratory Abnormalities during Phase 3

	INCIDENCE (%)	
LAB MEASUREMENT	Placebo	Aripiprazole
NUMBER OF PATIENTS IN SAFETY SAMPLE	166	167
CHEMISTRY		
Alkaline Phosphatase (U/L)	2/ 166 (1.2)	0/ 165
Alanine Aminotransferase (U/L)	3/ 166 (1.8)	3/ 165 (1.8)
Aspartate Aminotransferase (U/L)	0/ 166	0/ 165
Blood Urea Nitrogen (mg/dL)	3/ 139 (2.2)	1/ 138 (0.7)
Creatine Kinase (U/L)	8/ 166 (4.8)	6/ 165 (3.6)
Creatinine (mg/dL)	0/ 166	1/ 164 (0.6)
Lactate Dehydrogenase (U/L)	0/ 166	0/ 164
Prolactin (ng/mL)	14/ 163 (8.6)	14/ 158 (8.9)
Bilirubin Total (mg/dL)	2/ 166 (1.2)	3/ 165 (1.8)
Uric Acid (mg/dL)	4/ 166 (2.4)	7/ 165 (4.2)
ELECTROLYTES		
Total Calcium (mg/dL)	4/ 166 (2.4)	7/ 165 (4.2)
Chloride Serum (mEq/L)	1/ 166 (0.6)	1/ 165 (0.6)
Potassium Serum (mEq/L)	0/ 166	3/ 164 (1.8)
Sodium Serum (mEq/L)	1/ 166 (0.6)	1/ 165 (0.6)
HEMATOLOGY		
Hematocrit (%)	7/ 166 (4.2)	8/ 164 (4.9)
Hemoglobin (g/dL)	2/ 166 (1.2)	4/ 164 (2.4)
Leukocytes (x10*3 c/uL)	5/ 166 (3.0)	3/ 164 (1.8)
Eosinophils rel. (calc) (%)	6/ 166 (3.6)	11/ 164 (6.7)
Neutrophils rel. (calc) (%)	0/ 166	0/ 164
Platelet Count (x10*9 c/L)	0/ 165	0/ 162
URINALYSIS		
Urine Glucose	8/ 166 (4.8)	8/ 165 (4.8)
Urine Protein	5/ 166 (3.0)	4/ 165 (2.4)

METABOLIC					
Glucose (non-fast.) (mg/dL)	1/ 38	(2.6)	0/ 28		
Glucose (fast.) (mg/dL)	26/ 159	(16.4)	27/ 158	(17.1)	
HDL Cholesterol (comb.) (mg/dL)	81/ 166	(48.8)	91/ 165	(55.2)	
HDL Cholesterol (fast.) (mg/dL)	76/ 160	(47.5)	88/ 159	(55.3)	
HDL Cholesterol (non-fast.) (mg/dL)	20/ 38	(52.6)	11/ 27	(40.7)	
Total Cholesterol (comb.) (mg/dL)	28/ 166	(16.9)	38/ 165	(23.0)	
Total Cholesterol (fast.) (mg/dL)	27/ 160	(16.9)	35/ 159	(22.0)	
Total Cholesterol (non-fast.) (mg/dL)	3/ 38	(7.9)	7/ 27	(25.9)	
LDL Cholesterol (comb.) (mg/dL)	24/ 166	(14.5)	23/ 165	(13.9)	
LDL Cholesterol (fast.) (mg/dL)	24/ 160	(15.0)	22/ 159	(13.8)	
LDL Cholesterol (non-fast.) (mg/dL)	1/ 38	(2.6)	3/ 27	(11.1)	
Triglycerides (comb.) (mg/dL)	59/ 166	(35.5)	67/ 165	(40.6)	
Triglycerides (non-fast.) (mg/dL)	16/ 38	(42.1)	15/ 28	(53.6)	
Triglycerides (fast.) (mg/dL)	48/ 160	(30.0)	63/ 159	(39.6)	

7.4.3 Vital Signs

Supine and standing/sitting arterial systolic and diastolic blood pressure and radial artery pulse rate were measured at the scheduled visits designated in the protocol. Measurements were made after the patient had been supine for 5 minutes. The patient then stood up and repeat measurements were taken after standing 2 minutes. Vital signs that were scheduled at the same visit as blood samples were to be completed before blood was drawn.

There were no clinically relevant pattern of vital sign abnormalities in the treatment groups. The median change in Systolic and Diastolic BP from baseline to week 52 was similar in both the ABILIFY and placebo groups, except a decrease in sitting diastolic BP in the ABILIFY group of 2 mm Hg. For heart rate, the median change from baseline to week 52 was similar between the placebo group and 1 for the ABILIFY group, except the sitting heart rate, which decreased by -4 in the placebo group and -2 in the ABILIFY group.

Table 25: Number of Patients with potentially clinically relevant vital sign abnormalities during Phase 3.

	INCIDENCE (%)	
VITAL SIGN MEASUREMENT	Placebo	Aripiprazole
NUMBER PATIENTS IN SAFETY SAMPLE	166	167
Systolic Blood Pressure		
Standing Increase	0/ 145	0/ 147
Standing Decrease	2/ 145 (1.4)	1/ 147 (0.7)
Supine Increase	0/ 165	0/ 164
Supine Decrease	2/ 165 (1.2)	2/ 164 (1.2)
Sitting Increase	0/ 41	0/ 47
Sitting Decrease	0/ 41	1/ 47 (2.1)
Diastolic Blood Pressure		
Standing Increase	5/ 145 (3.4)	1/ 147 (0.7)
Standing Decrease	0/ 145	2/ 147 (1.4)
Supine Increase	4/ 165 (2.4)	3/ 164 (1.8)
Supine Decrease	1/ 165 (0.6)	2/ 164 (1.2)
Sitting Increase	1/ 41 (2.4)	0/ 47
Sitting Decrease	0/ 41	0/ 47
Heart Rate		
Standing Increase	1/ 145 (0.7)	1/ 147 (0.7)
Standing Decrease	2/ 145 (1.4)	0/ 147
Supine Increase	0/ 165	0/ 164
Supine Decrease	1/ 165 (0.6)	1/ 164 (0.6)
Sitting Increase	0/ 41	0/ 47
Sitting Decrease	0/ 41	1/ 47 (2.1)

7.4.4 Electrocardiograms (ECGs)

A standard 12-lead ECG was recorded at the Screening visit (beginning of Phase 1); Week 24/End of Phase 2 visit; and Weeks 24 (for lithium patients only) and 52/Early Termination in Phase 3. Two additional ECGs for United States (US) patients (Week 8/End of Phase 1 and Phase 2, Week 4) were added at the request of the Food and Drug Administration (FDA). A central ECG service was utilized for reading all ECGs.

There were no QTcB or QTcF of > 500 msec in the placebo group and two in the aripiprazole group.

A total of 8.2% of patients receiving placebo and 10% receiving aripiprazole had a QTcB of >450 msec, and the incidence of QTcF >450 msec was 3.4% for placebo-treated patients and 2.7% for aripiprazole-treated patients.

The change from baseline in QTcB was 13.7% in the placebo group and 16.7% in the aripiprazole group. Change in QTcF of > 30 msec was 6.8% in placebo-treated patients and 13.3% in aripiprazole-treated patients.

Change in QTcB >60 msec was 2.1% in the placebo group and 2.7% in the aripiprazole group and QTcF was 1.4% in the placebo group and 2.0% in the aripiprazole group.

Analysis of change in QTc by lithium or valproate patients showed that 6.4% of patients on lithium and 2.6% of patients on valproate had QTcB> 450 msec, whereas 2.1% of patients on lithium and 0.6% on valproate had QTcF>450 msec. Changes in QTcB > 30 msec were seen in 11.9% on lithium, 5.4% on valproate, and QTcF > 30 msec were seen in 8.9% and 3.5% on lithium and valproate respectively.

Patient CN138189-119-804, a 46-year-old white male receiving aripiprazole 15 mg and lithium 1000 mg, had a > 500 msec QTcB and QTcF at the Week 52 visit (baseline values were 453 and 457, respectively).The QTcB/QTcF abnormality was not recorded as an AE by the investigator and the patient subsequently completed the study.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

Body Weight and Body Mass Index

No significant differences between the placebo and aripiprazole treatment groups were reported in the adjusted mean change in patient body weight from baseline to Week 52 (LOCF) or highest value. There were also no differences in clinically relevant weight gain (≥7% increase from baseline) or body weight loss (≥7% decrease from baseline).

7.5.1 Dose Dependency for Adverse Events

Not analyzed

7.5.2 Time Dependency for Adverse Events

Not analyzed

7.5.3 Drug-Demographic Interactions

None

7.5.4 Drug-Disease Interactions

None

7.5.5 Drug-Drug Interactions

None

7.6 Additional Safety Evaluations

None

7.6.1 Human Carcinogenicity

Not applicable

7.6.2 Human Reproduction and Pregnancy Data

In the Enrolled Sample, a total of 12 pregnancies were reported:

- Screening: 5 patients
- Phase 1; 2 patients: 1 lithium-treated patient; 1 valproate-treated patient
- Phase 2; 1 patient receiving lithium and aripiprazole
- Phase 3; 4 patients: 1 valproate/aripiprazole-treated patient;
  2 valproate/placebo-treated patients; and 1 lithium/placebo-treated patient)

Reviewer's Comments: I reviewed the narratives of the four patients in Phase 3, who became pregnant. In all instances, the patients were discontinued from the study when the pregnancy test became positive. The result of one of the patients (VPA+Aripiprazole) was thought to be a false positive result as she was negative when retested. One of the patients on valproate (VPA+ abilify) was discontinued from the study and underwent an induced abortion, while the patient who became pregnant on VPA+PBO had a medical termination of pregnancy. The patient on abilify +lithium was lost to follow up.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

One patient each in Phase 2 and Phase 3 attempted suicide by an overdose.

In Phase 3, Patient CN138189-25-151, a 32-year-old white female receiving valproate 750 mg and aripiprazole 30 mg, reported a very severe suicide attempt by overdose. The subject took 5250 mg of valproate and 60 mg of aripiprazole impulsively to kill herself. She was taken to the emergency room and study medication was discontinued. No medical treatment for the overdose was given and there were no clinically relevant vital sign, laboratory or ECG abnormalities. Her condition was reported as resolved without sequale 5 days later. The patient was discontinued from study drug on Phase 3 Day 158.

In Phase 2, Patient CN138189-89-448, a 24-year-old male receiving valproate 1000 mg and aripiprazole 15 mg, reported a suicide attempt on Phase 2 Day 53. The patient was discontinued from study drug due to this event. The patient was admitted to the hospital and gastric lavage was conducted and was discharged the next day.

No data has been submitted regarding abuse potential, withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

The sponsor submitted a Periodic Drug Adverse Experience Report for the period from 1-Nov-2009 through 31-Oct-2010. The sponsor did not identify any new safety issues. I reviewed the report and I concur with the sponsor's assessment.

8 Postmarket Experience

ABILIFY has been marketed in the United States since 2002.

9 Appendices

9.1 Literature Review/References

The sponsor conducted a worldwide literature search for published articles pertaining to the safety and efficacy of aripiprazole in bipolar disorder was conducted. The literature search timeframe includes published articles from June 30, 2008 through a cut-off date of December 31, 2009. A total of 434 articles were identified and reviewed.

The sponsor concluded that 'the literature contains no findings that would adversely affect conclusions about the safety and efficacy of aripiprazole contained in supplemental submission for adjunctive bipolar disorder.'

9.2 Labeling Recommendations

The major labeling reviews have been summarized as follows.

1. Dosage and Administration

The sponsor has proposed adding details of the adjunctive maintenance treatment for bipiolar disorder. However, a detailed description of the study is already given under section 14. This section has hence been shortened.

2. Clinical Studies

Under section 14.2, Bipolar Disorder, additional details have been included in the section on adjunctive therapy, including the addition of a Kaplan-Meier estimation of the proportion of relapses to any mood event.

9.3 Advisory Committee Meeting

Not applicable

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/s/

MAJU MATHEWS
01/25/2011

JING ZHANG
01/26/2011