Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597)

Clinical Summary for Protocol 31-03-240

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Two Fixed Oral Doses of Aripiprazole (10 mg and 30 mg) in the Treatment of Child and Adolescent Patients, Ages 10-17 Years, with Bipolar I Disorder, Manic or Mixed Episode with or without Psychotic Features**$NCT No. 00110461**

Indication: Bipolar I Disorder

Clinical Development Phase: 3

Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Boulevard
Rockville, Maryland US

Trial Initiation Date: 30 Mar 2005
Trial Completion Date: 16 Feb 2007
Summary Issued: 23 Dec 2014

This summary is for public dissemination of information in accordance with local regulatory requirements.
These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert.
This trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the institutional review board or ethics committee at each respective trial center.

Name of Investigational Medicinal Product: Aripiprazole (OPC-14597)

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Two Fixed Oral Doses of Aripiprazole (10 mg and 30 mg) in the Treatment of Child and Adolescent Patients, Ages 10-17 Years, with Bipolar I Disorder, Manic or Mixed Episode with or without Psychotic Features

Trial Centers by Region: 59 centers in the US

Clinical Phase/Trial Type: 3/Interventional

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale:

Aripiprazole, OPC-14597, is approved and marketed for the treatment of adults with acute schizophrenia (as of November 2002), maintenance of stability in schizophrenia (as of August 2003), treatment of bipolar I disorder, manic or mixed episode, with or without psychotic features (as of September 2004), and for the maintenance of efficacy in bipolar I disorder (as of March 2005) in the United States (US). Aripiprazole is currently approved for the treatment of schizophrenia in the European Union, Australia, and a number of countries in Asia, Europe, and Latin America. The safety of aripiprazole tablets has been studied in approximately 8456 adult subjects to date.[1] Please refer to the Investigator Brochure[2,3,4,5,6] and the US Abilify package insert[1] for detailed information on preclinical and adult clinical data.

The aripiprazole pediatric efficacy program (APEX) was designed by Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC) in response to the US Food and Drug Administration (FDA) Pediatric Written Request (PWR) dated 11 February 2003, and is intended to provide controlled clinical data for the use of aripiprazole for the treatment of schizophrenia and bipolar I disorder in the pediatric population. An additional objective is to provide information about the PK of aripiprazole in the pediatric population. The APEX program is composed of four studies: one open-label sequential cohort (20 mg, 25 mg, 30 mg) safety, tolerability, and pharmacokinetic (PK) trial (31-03-238) in pediatric in-patient subjects with psychiatric disorders;[7] one randomized, double-blind, placebo-controlled, fixed dose (10 mg and 30 mg), acute safety and efficacy trial in schizophrenia subjects (31-03-239, aged 13 to 17 years);[8] one 30-week, randomized, double-blind, placebo-controlled, fixed dose (10 mg and 30 mg) trial in bipolar mania subjects (31-03-240, aged 10 to 17 years);[9] and a roll-over, open-label, flexible dose safety trial in both schizophrenia and bipolar subjects (31-03-241, aged 10 to 17 years) who either completed OPDC Trial 31-03-239 or withdrew from the extension phase of OPDC Trial 31-03-240. There is also a population PK report. A fifth trial (open-label trial 31-03-243) was instituted to provide compassionate aripiprazole therapy to subjects with

schizophrenia completing this open-label safety trial (31-03-241) in countries where aripiprazole is not yet
available

Publications:

Youngstrom E, Zhao J, Mankoski R, Forbes RA, Marcus RM, Carson W, McQuade R, Findling RL. Clinical significance of treatment effects with aripiprazole versus placebo in a study of manic or mixed episodes associated with pediatric bipolar I disorder. J Child Adolesc Psychopharmacol. 2013 Mar;23(2):72-9.

Findling RL, Correll CU, Nyilas M, Forbes RA, McQuade RD, Jin N, Ivanova S, Mankoski R, Carson WH, Carlson GA. Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study. Bipolar Disord. 2013 Mar;15(2):138-49.

Mankoski R, Zhao J, Carson WH, Mathew SJ, Forbes RA. Young mania rating scale line item analysis in pediatric subjects with bipolar I disorder treated with aripiprazole in a short-term, double-blind, randomized study. J Child Adolesc Psychopharmacol. 2011 Aug;21(4):359-64.

Findling RL, Nyilas M, Forbes RA, McQuade RD, Jin N, Iwamoto T, Ivanova S, Carson WH, Chang K. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2009 Oct;70(10):1441-51.

Objectives: The primary objective of the trial was to compare the efficacy of two fixed doses of aripiprazole (10 mg and 30 mg) to placebo, and to assess the safety of aripiprazole in children and adolescent subjects, ages 10 to 17 years, with bipolar I disorder, manic or mixed episode with or without psychotic features.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in child and adolescent subjects ages 10 to 17 years, with a Diagnostic and Statistical Manual IV (DSM-IV) diagnosis of bipolar I disorder, manic or mixed episode with or without psychotic features. The initial diagnosis was made by an adequately trained clinician (ie, board certified child and adolescent psychiatrist [CAP] or board eligible CAP), and then confirmed by an adequately trained clinician utilizing the Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version (K-SADS-PL) at screening. There were two phases in this trial, an Acute Phase and an Extension Phase. Both phases of the trial could be conducted either on an outsubject basis (with the option for insubject hospitalization, if needed), or in a partial or full insubject basis at any given time of the trial. Subjects who received at least one dose of trial medication in the Extension Phase

of the trial were eligible to roll-over to an open label trial (Trial No. 31-03-241) if they dropped out of this phase due to tolerability reasons.

Subjects were randomized on Day 1 to either 10 mg or 30 mg of oral aripiprazole or placebo. Subjects reached their target dose through a forced titration schedule and proceeded with treatment at their target dose until Week 4, as follows:

- Subjects in the 10 mg treatment arm received aripiprazole 2 mg/day for 2 days, aripiprazole 5 mg/day for 2 days, and aripiprazole 10 mg/day as the target dose starting on Day 5. Subjects remained on the 10 mg dose for the remainder of the Acute Phase treatment period.
- Subjects in the 30 mg treatment arm received aripiprazole 2 mg/day for 2 days, aripiprazole 5 mg/day for 2 days, aripiprazole 10 mg/day for 2 days, aripiprazole 15 mg/day for 2 days, aripiprazole 20 mg/day for 2 days, aripiprazole 25 mg/day for 2 days, and aripiprazole 30 mg/day as the target dose starting on Day 13. Subjects remained on the 30 mg dose for the remainder of the Acute Phase treatment period.
- Subjects in the placebo arm received matching placebo.

If the subject reached Week 4 of the Acute Phase, they continued into the Extension Phase, a 6-month double-blind treatment period, beginning at the same dose taken at the end of the Acute Phase. The investigator had the option to down-titrate a subject's dose only one time during the Extension Phase to half the target dose for tolerability reasons (ie, down to 15 mg for the 30 mg arm and down to 5 mg for 10 mg arm). Following a dose reduction, investigators could also up-titrate one time as needed to enhance efficacy as follows: to 20 mg from 15 mg in the 30 mg arm, and to 10 mg from 5 mg in the 10 mg arm. Subjects who discontinued during the Acute Phase for lack of efficacy, or for any reason, were offered an alternative rescue medication for 4 to 8 weeks.

Mandatory subject evaluations took place during the Acute Phase at Day 1 (Baseline), (phone call at Day 4), and at Weeks 1, 2, 3, and 4, and during the Extension Phase at Weeks 6, 8, 10, 12, 16, 20, 24, and 30. In addition, subjects were contacted by telephoneat the end of every odd week after Week 4 (ie, Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23,25, 27, and 29) to assess medication compliance and assure the subject's well-being. An independent data safety monitoring board reviewed and evaluated cumulative safety data collected at regular intervals to ensure the safety of subjects enrolled in all aripiprazole pediatric trials.

Number of Subjects: A minimum of 330 subjects at approximately 60 sites in the United States were planned for screening into the trial, with the expectation that approximately 290 subjects would be randomized to yield at least 261 (87 per treatment arm) evaluable subjects. A total of 413 subjects were screened, and 296 subjects were randomized at 59 sites.

Diagnosis and Main Criteria for Inclusion: Male and female subjects, ages 10 to 17 years, with a K-SADS-PL confirmed Axis I (DSM-IV) diagnosis of bipolar I disorder, manic or mixed episode with or without psychotic features, who had a Young Mania Rating Scale (Y-MRS) score of ≥ 20 at Baseline (Day 1).

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Aripiprazole oral tablets (2 mg, 5 mg, 10 mg, and 15 mg). Doses were as follows:

- Aripiprazole 2 mg tablets, dosed 2 mg/day
- Aripiprazole 5 mg tablets, dosed 5 mg/day
- Aripiprazole 10 mg tablets, dosed 10 mg/day
- Aripiprazole 15 mg tablets, dosed 15 mg/day
- Aripiprazole 10 mg tablets, dosed 20 mg/day
- Aripiprazole 10 mg tablets and 15 mg tablets, dosed 25 mg/day
- Aripiprazole 15 mg tablets, dosed 30 mg/day

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Placebo was identical in appearance and was dosed identically to the active drug within each treatment group.

Duration of Treatment: Each subject had the potential to participate in this trial for a total of up to 30 weeks of double-blind treatment, including a 4-week acute phase with a 6-month extension period, preceded by a screening phase of up to 28 days.

Trial Assessments: Trial assessments included efficacy, safety, and other outcome variables both for the acute phase and also for the extension phase.

Criteria for Evaluation:
Acute Phase

Efficacy:

Primary Efficacy Endpoint: The primary efficacy endpoint for the Acute Phase was the change from baseline to Week 4 in the Y-MRS total score.

Secondary Efficacy Endpoints: Secondary efficacy endpoints for the Acute Phase were the following:
Change from baseline (evaluated at each visit) in the:

- Y-MRS total score
- The Children's Global Assessment Scale (CGAS) score
- Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity score
- The Children's Depression Rating Scale-Revised (CDRS-R) score
- The General Behavior Inventory Scale (GBI) score
- The Attention Deficit Hyperactivity Disorders Rating Scale (ADHD-RS-IV) score

In addition:

- Subjects response to treatment (defined as a 50% or higher reduction from baseline in Y-MRS total score)
- Change from preceding phase score on the CGI-BP
- Time to discontinuation due to all reasons

Safety:

The following safety endpoints were evaluated:

- The frequency by severity of adverse events (AEs), serious adverse events (SAEs) (clinical and laboratory), and discontinuation from the trial due to AEs through Week 4
- Change from baseline through Week 4 (Acute Phase) on the Simpson-Angus Scale (SAS) score, Abnormal Involuntary Movement Scale (AIMS) score, and Barnes-Akathisia Rating Scale (BARS) score
- Change from baseline in: vital signs parameters (supine and standing positions); electrocardiogram (ECG) parameters; serum prolactin concentrations; routine laboratory tests (including creatine phosphokinase [CPK]) results; and listing of physical examination findings through Week 4
- Percentage of subjects showing significant weight gain or loss from randomization through Week 4 (≥ 7% increase or decrease in weight)
- Change from baseline through Week 4 in body mass index (BMI), waist circumference, blood pressure, and fasting levels of insulin, triglycerides, high-density lipoproteins, and glucose.

Other Outcome Variables:
The following additional endpoints were evaluated for the Acute Phase:

- Change from baseline in the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) score at Week 4
- The number of hospitalizations for each randomized subject through Week 4

Extension Phase

Efficacy:

The efficacy endpoints for the Extension Phase were the following:
Change from baseline (evaluated at each visit up to Week 30) in the:

- Y-MRS total score
- CGAS score
- Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity score
- The Children's Depression Rating Scale-Revised (CDRS-R) score
- The General Behavior Inventory Scale (GBI) score
- The Attention Deficit Hyperactivity Disorders Rating Scale (ADHD-RS-IV) score

In addition:

- Subject response to treatment (defined as a 50% or higher reduction from baseline in Y-MRS total score)
- Change from preceding phase score on the CGI-BP
- Time to discontinuation due to all reasons

Safety:
The following safety endpoints were evaluated:

- The frequency by severity of AEs, SAEs (clinical and laboratory), and discontinuation from the trial due to AEs up to Week 30
- Change from baseline by visit up to Week 30 on the SAS score, AIMS score, and BARS score
- Change from baseline in: vital sign parameters (supine and standing positions); ECG parameters; serum prolactin concentrations, routine laboratory tests (including CPK) results; and listing of physical examination findings by visit up to Week 30
- Percentage of subjects showing significant weight gain or loss from randomization by visit up to Week 30 (≥ 7% increase or decrease in weight)
- Change from baseline by visit up to Week 30 in BMI, waist circumference, blood pressure, and fasting levels of insulin, triglycerides, high-density lipoproteins, and glucose

Other Outcome Variables:
The following additional endpoints were evaluated:

- Change from baseline in the P-QLES-Q score by visit up to Week 30
- The number of hospitalizations for each randomized subject up to Week 30

Statistical Methods:

Acute Phase: The Acute Phase of the trial was defined as the first 4 weeks of treatment after randomization. A primary objective of this trial was to demonstrate the efficacy of aripiprazole in the treatment of bipolar I disorder, manic or mixed episode, with or without psychotic features, during this Acute Phase. Hence, the efficacy results presented for these first 4 weeks correspond to results for the Acute Phase. Similarly, the safety results presented for these first 4 weeks correspond to results of the Acute Phase.

Extension Phase: The Extension Phase of the trial was defined as beyond the Week 4 visit through the Week 30 visit. These additional 26 weeks were added to the trial period in order to evaluate the long term safety of the drug. Hence, the treatment period for evaluating long term safety was 30 weeks, ie, all post-baseline evaluations up to Week 30.

For both the Acute Phase and Extension Phase, where efficacy and safety evaluations were performed by visit (week), summary results were presented by week. For example,

mean change from baseline in Y-MRS score, vital signs, laboratory values, etc, were presented by week from Week 1 through Week 30.

A nominal overall significance level of 0.05 (two-tailed) was used in testing the statistical significance of the comparisons between aripiprazole 10 mg target dose versus placebo and aripiprazole 30 mg target dose versus placebo. For the primary treatment comparisons of a dose group versus placebo, adjustment in testing due to multiple comparisons was handled by an overall F-test. Descriptive statistics for the Y-MRS total scores and change from baseline scores were presented by treatment group for Week 1 through Week 4 for both observed case (OC) and last observation carried forward (LOCF) datasets. The change scores were analyzed by using an analysis of covariance (ANCOVA) model with treatment as a factor, and baseline Y-MRS total score as a covariate. For comparing Y-MRS total scores between treatment groups at baseline, only treatment was included in the analysis of variance (ANOVA) model with baseline value as the dependent variable. The least squares (LS) means obtained from a type III analysis using SAS were used for the treatment comparisons. Two-tailed student's t-tests were used to test differences between the LS means within the ANCOVA or ANOVA model. The CGAS, CGI-BP severity, CDRS-R, GBI, ADHD-RS-IV, and P-QLES-Q total score were analyzed similarly to the Y-MRS. The proportion of subjects responding to treatment was analyzed using a chi-square test, with 95% confidence intervals for differences in response rates. Changes from the preceding phase score in the CGI-BP and P-QLES-Q overall score were analyzed using the Cochran-Mantel-Haenszel row mean score statistic by week. Time to discontinuation was analyzed by plotting the Kaplan-Meier curves and testing for significance of the differences in survival curves using the log-rank test for each active group versus the placebo group. All safety variables were listed and, where appropriate, summarized by descriptive statistics (proportion, mean, median, standard deviation (SD), minimum, and maximum). Two pairwise comparisons between the aripiprazole groups and the placebo group for ECG parameters at scheduled visits were performed based on an ANCOVA model with baseline ECG parameter as a covariate and treatment as a factor. Changes from baseline in SAS total score, BARS global score, and AIMS scores were analyzed by ANCOVA with treatment group as a factor and baseline as a covariate.

Pharmacokinetic/pharmacodynamic Methods: Blood sampling for population pharmacokinetic analysis was performed at Days 1 (Baseline), and at Weeks 1, 2, 3 and 4 during the Acute Phase. A single 4 mL sample was obtained at pre-dose on Day 1 and Weeks 1, 2, 3 and 4 during the Acute Phase. Plasma concentrations of aripiprazole and OPC-14857 were simultaneously measured by a validated high performance liquid chromatography method with tandem mass spectrophotometic detection. The concentration data will be combined with other studies in a population pharmacokinetic analysis, to be reported separately.

Summary of Results:

Baseline Data, Disposition, and Demographics: A total of 413 subjects were screened, and 296 subjects were randomized in this trial: 98 in the aripiprazole 10 mg arm, 99 in the aripiprazole 30 mg arm, and 99 in the placebo arm. A total of 294 subjects were treated (2 subjects from the placebo arm did not receive trial drug). Demographics were similar across treatment arms. The mean age was 13.43 years (SD ± 2.21; range, 10 to 17 years). The majority of subjects were Caucasian/white: 66.33% (65/98 subjects) in the aripiprazole 10 mg arm, 68.69% (68/99 subjects) in the aripiprazole 30 mg arm, and 60.61% (60/99 subjects) in the placebo arm. Hispanic/Latino subjects accounted for 6.12% of subjects (6/98 subjects) in the 10 mg arm, 10.10% (10/99 subjects) in the 30 mg arm, and 15.15% (15/99 subjects) in the placebo arm. The percentages of Black/African American subjects were 24.49% (24/98 subjects) in the 10 mg arm, 18.18% (18/99 subjects) in the 30 mg arm, and 23.23% (23/99 subjects) in the placebo arm. The other subjects were native Hawaiian or other Pacific Islander, or "other" races. Baseline disease characteristics based on Y-MRS Total Score (mean baseline score ranged from 29.5 to 30.7), CDRS-R Suicidal Ideation Score, and treatment for previous episodes were also similar across treatment arms. For the combined aripiprazole arms at baseline, 13.7% (27/197) of subjects had a score of 5, 6, or 7 on the CGI-BP severity score for depression, compared with 13.1% (13/99) of subjects in the placebo arm.

Efficacy Results:

Primary Efficacy:

Y-MRS Total Score at Week 4:

In this trial, aripiprazole 10 mg and 30 mg were effective in the treatment of bipolar disorder with manic episodes based on the change in Y-MRS Total Score from baseline to Week 4 (the primary efficacy endpoint). Both aripiprazole doses showed statistically significant improvements over placebo in the Y-MRS Total Score at Week 4 using both the LOCF and OC data sets, as shown in the following table. Using the LOCF data set, the Y-MRS Total Score changes from baseline to Week 4 were −14.2 in the aripiprazole 10 mg arm, −16.5 in the 30 mg arm, and −8.2 in the placebo arm. The comparison between aripiprazole and placebo was significant at both doses ($p < 0.0001$ for both). Similar trends were observed in the analysis using the OC data set, with changes from baseline to Week 4 of −15.0 in the aripiprazole 10 mg arm, −17.1 in the 30 mg arm, and −9.2 in the placebo arm ($p < 0.0001$ for both treatment comparisons).

Mean Change From Baseline in Y-MRS Total Score by Week - Acute Phase (LOCF and OC)

Visit/Week	Aripiprazole 10 mg N	Aripiprazole 10 mg LS Mean[a]	Aripiprazole 30 mg N	Aripiprazole 30 mg LS Mean[a]	Placebo N	Placebo LS Mean[a]	P-value[b] Aripiprazole 10 mg vs placebo	P-value[b] Aripiprazole 30 mg vs placebo
Baseline[c]	96	29.8	99	29.5	94	31.1	0.1702	0.0916
LOCF								
Week 1	92	-9.0	95	-9.4	87	-5.6	0.0023	0.0006
Week 2	94	-12.8	99	-13.7	92	-7.7	<0.0001	<0.0001

Week 3	96	-13.9	99	-15.0	92	-8.1	<0.0001	<0.0001
Week 4[d]	96	-14.2	99	-16.5	92	-8.2	<0.0001	<0.0001
Treatment Difference at Week 4 [95% CI]							-5.99 [-8.49 to -3.50]	-8.26 [-10.7 to -5.77]
OC								
Week 1	92	-9.0	95	-9.4	87	-5.6	0.0023	0.0006
Week 2	82	-12.8	87	-14.7	81	-8.3	0.0004	<0.0001
Week 3	83	-14.5	75	-16.6	74	-8.9	<0.0001	<0.0001
Week 4	78	-15.0	75	-17.1	67	-9.2	<0.0001	<0.0001
Treatment Difference at Week 4 [95% CI]							-5.81 [-8.51 to -3.12)	-7.92 [-10.6 to -5.20]

vs = versus

[a]The LS means are the adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and term for treatment. A negative LS mean indicated improvement.

[b]The p-values were derived from Student's t tests on estimates of treatment comparisons which were based on LS means.

[c]For baseline, N and Mean are provided.

[d]Primary endpoint.

Secondary Efficacy:

Aripiprazole was also consistently effective in the treatment of bipolar disorder in adolescents in this trial based on a variety of secondary efficacy endpoints including changes from baseline at each visit for Y-MRS total score, CGAS score, CGI-BP severity score, GBI score, CDRS-R score, and ADHD-RS-IV score; subject response to treatment (defined as a 50% or higher reduction from baseline in Y-MRS total score); changes from preceding phase score on the CGI-BP; and time to discontinuation due to all reasons.

Y-MRS Total Score at Each Visit:

Aripiprazole 10 mg and 30 mg showed statistically significant improvements over placebo in the change from baseline in Y-MRS Total Score at all weeks up to Week 30; ($p < 0.0001$ at all visits) using LOCF. Mean changes in Y-MRS Total Scores at Week 30 were −14.1 in the aripiprazole 10 mg arm, −14.9 in the aripiprazole 30 mg arm, and −8.2 in the placebo arm; treatment differences were −5.89 (95% confidence interval [CI] = −8.70 to −3.08; $p < 0.0001$) for the aripiprazole 10 mg arm and −6.73 (95% CI = −9.53 to −3.94; $p < 0.0001$) for the aripiprazole 30 mg arm.

Responders:

Both the aripiprazole 10 mg and 30 mg arms had significantly higher percentages of responders (subjects with a ≥ 50% reduction from baseline in Y-MRS Total Score) compared to the placebo arm at every treatment week during both the Acute Phase and during the entire 30-week period using the LOCF data set. At Week 4 (end of the Acute Phase), the percentages of responders using LOCF were 44.79%, 63.64%, and 26.09% in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0074$ for 10 mg versus placebo [95% CI = 5.01 to 32.40] and $p < 0.0001$ for 30 mg versus placebo [95% CI = 23.41 to 51.68]). At Week 30, the percentages of responders using LOCF (last visit)

were 50.00%, 55.56%, and 26.60% in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0009$ for 10 mg versus placebo and $p < 0.001$ for 30 mg versus placebo).

CGAS Score:
Both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm in the change from baseline in CGAS Score at the end of the Acute Phase (Week 4) and at Week 30 using the LOCF data set. At Week 4 (end of the Acute Phase), the mean changes from baseline using LOCF were 15.1, 17.3, and 5.8 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p < 0.0001$ for both comparisons). Statistically significant differences between the aripiprazole 10 mg and 30 mg treatment arms versus placebo were also observed beginning at the first assessment (Week 1) and at every treatment visit during the Acute Phase. Statistically significant differences between the aripiprazole 10 mg arm versus placebo and the aripiprazole 30 mg arm versus placebo were observed at all visit weeks up to Week 30. Similar results were observed for the Acute Phase, and numeric improvements were observed through Week 6 to Week 30 using the OC data set.

CGI-BP Severity Score:
Changes from baseline in CGI-BP severity scores were evaluated for mania, depression, and overall bipolar illness. Both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm in the change from baseline in CGI-BP severity score for mania and for overall bipolar illness at the end of the Acute Phase (Week 4) and at Week 30 using the LOCF data set.

At Week 4, the mean changes from baseline in CGI-BP severity score for mania using LOCF were −1.6, −2.1, and −0.8 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p < 0.0001$ for 10 mg versus placebo and for 30 mg versus placebo). Statistically significant differences between the aripiprazole 10 mg and 30 mg arms versus placebo were also observed beginning at Week 1, and at every treatment visit during the Acute Phase. At Week 30, the mean changes from baseline in CGI-BP severity score for mania using LOCF were −1.7, −2.0, and −0.9 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0003$ for 10 mg versus placebo and $p < 0.0001$ for 30 mg versus placebo). Similar results were seen for the Acute Phase and numeric improvements were seen through Week 6 to Week 30 using the OC data set.

At Week 4, the mean changes from baseline in CGI-BP severity score for overall bipolar illness using LOCF were −1.6, −2.0, and −0.8 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p < 0.0001$ for 10 mg versus placebo and for 30 mg versus placebo). Statistically significant differences between the aripiprazole 10 mg and 30 mg arms versus placebo were also observed beginning at Week 1, and at every treatment visit during the Acute Phase. At Week 30, the mean changes from baseline using LOCF were −1.7, −2.0, and −0.9 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0003$ for 10 mg versus placebo and $p < 0.0001$ for 30 mg versus placebo). Similar

results were seen in the Acute Phase and numeric improvements were seen through Week 6 to Week 30 using the OC data set.

No statistically significant differences in mean changes in CGI-BP severity score for depression between the aripiprazole 10 mg arm and placebo or the aripiprazole 30 mg arm and placebo were observed at any time during the Acute Phase of the trial (LOCF).

Mean changes from baseline at Week 4 were −0.9, −0.9, and −0.6 in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms, respectively. At Week 30, the mean change from baseline was statistically significant for the 30 mg versus placebo comparison ($p = 0.0166$).

CGI-BP Change from Preceding Phase Score:
Mean changes from the preceding phase score were also analyzed for CGI-BP scores for mania, depression, and overall bipolar illness.

Both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm in the change from preceding phase score in CGI-BP score for mania and for overall bipolar illness at the end of the Acute Phase (Week 4) and at Week 30 using the LOCF data set. At Week 4, the mean changes from the preceding phase score for CGI-BP for mania were 2.4, 2.3, and 3.4 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p < 0.0001$ for 10 mg versus placebo and for 30 mg versus placebo); at Week 30, the mean changes were 2.6, 2.5, and 3.3 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0020$ for 10 mg versus placebo and $p = 0.0001$ for 30 mg versus placebo).

At Week 4, the mean changes from the preceding phase score in CGI-BP for overall bipolar illness using LOCF were 2.5, 2.4, and 3.5 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p < 0.0001$ for 10 mg versus placebo and for 30 mg versus placebo); at Week 30, the mean changes were 2.8, 2.6, and 3.4 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0030$ for 10 mg versus placebo and $p = 0.0001$ for 30 mg versus placebo).

Both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm in the change from the preceding phase score in CGI-BP score for depression at the end of the Acute Phase (Week 4), and the aripiprazole 30 mg arm showed statistically significant improvements over the placebo arm at Week 30. At Week 4, the mean changes from the preceding phase score in CGI-BP for depression using LOCF were 3.0, 3.1, and 3.6 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0010$ for 10 mg versus placebo and $p = 0.0053$ for 30 mg versus placebo); at Week 30, the mean changes were 3.3, 3.1, and 3.6 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0113$ for 30 mg versus placebo).

CDRS-R Score:

There were no statistically significant differences between the aripiprazole 10 mg and placebo arms or the 30 mg and placebo arms in mean changes from baseline in CDRS-R Score at the end of the Acute Phase (Week 4) or at Week 30 using the LOCF or OC data sets. However, both the aripiprazole 10 mg and 30 mg arms showed numerically superior results compared to the placebo arm.

GBI Total Score:
Both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm in the change from baseline in GBI Total Score, Parent/Guardian Version for mania at the end of the Acute Phase (Week 4) using the LOCF and OC data sets, and at Week 30 using the LOCF data set. At Week 4, the mean changes from baseline using LOCF were −9.9, −9.5, and −4.0 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p < 0.0001$ for 10 mg versus placebo and for 30 mg versus placebo); at Week 30, the mean changes from baseline were −9.0, −8.9, and −4.3 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p < 0.0001$ for 10 mg versus placebo and for 30 mg versus placebo). Similar results were observed up to Week 8, and numerical superiority was seen in both aripiprazole groups in the following weeks up to Week 30 using the OC data set.

Both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm in the change from baseline in GBI Total Score, Subject Version for mania at the end of the Acute Phase (Week 4), and the 30 mg arm showed significant improvement over placebo at Week 30 using the LOCF data set. At Week 4, the mean changes from baseline using LOCF were −6.4, −6.6, and −4.6 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0468$ for 10 mg versus placebo and $p = 0.0296$ for 30 mg versus placebo); at Week 30, the mean changes from baseline using LOCF were −6.7, −7.9, and −5.3 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0058$ for 30 mg versus placebo). There were no statistically significant differences between the aripiprazole 10 mg arm or the 30 mg versus placebo at any time using the OC data set, but numerical superiority was observed in the aripiprazole groups up to Week 30.

For change from baseline in GBI Total Score, Parent/Guardian Version for depression, the aripiprazole 10 mg arm showed statistically significant improvements over the placebo arm at the end of the Acute Phase (Week 4), but not at Week 30 using the LOCF data set; differences between the 30 mg arm and placebo were not statistically significant during the 30-week trial (LOCF). At Week 4, the mean changes from baseline using

LOCF were −5.9, −4.1, and −3.8 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0430$ for 10 mg versus placebo); at Week 30, the mean changes from baseline were −5.0, −4.1, and −2.8 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively. There were only sporadic significant differences between aripiprazole and placebo throughout the trial using the OC data set.

For the GBI Total Score, Subject Version for depression, there were no statistically significant differences between the aripiprazole arms and placebo at any time during the entire trial period using either data set.

ADHD-RS-IV Total Score:
For the change from baseline in ADHD-RS-IV Total Score, both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm at the end of the Acute Phase (Week 4) using the LOCF and OC data sets and at the end of the Acute + Extension Phase (Week 30) using the LOCF data set. At Week 4, the mean changes from baseline using LOCF were −12.5, −11.9, and −3.7 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p < 0.0001$ for 10 mg versus placebo and for 30 mg versus placebo); at Week 30, the mean changes from baseline using LOCF were −11.6, −10.1, and −4.6 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p < 0.0001$ for 10 mg versus placebo and $p = 0.0014$ for 30 mg versus placebo). Similar results were observed using the OC data set for the Acute Phase only.

Time to Discontinuation:
No statistically significant differences were observed between the aripiprazole 10 mg arm and placebo or the aripiprazole 30 mg arm and placebo with respect to time to discontinuation due to all reasons during the Acute Phase. For the entire trial period, statistically significant differences in time to discontinuation due to all reasons were noted between both the aripiprazole 10 mg arm versus placebo ($p < 0.0001$) and 30 mg arm versus placebo ($p = 0.0124$). For both aripiprazole doses, the proportions of subjects remaining in the trial (as measured by the Kaplan-Meier curves) were superior to that of placebo. The median times that subjects remained in the trial were 109 days for the aripiprazole 10 mg arm, 66 days for the aripiprazole 30 mg arm, and 37 days for the placebo arm.

Pharmacokinetic/pharmacodynamic Results: The concentration data and calculated time postdose were reviewed for correctness; errors and discrepancies were noted and, if possible, corrections were noted.

Safety Results:
A total of 197 subjects were exposed to aripiprazole: 98 in the 10 mg arm, with an average dose of 8.6 mg overall (8.3 mg in the Acute Phase and 9.3 mg in the Extension Phase), and 99 in the 30 mg arm, with an average dose of 22.1 mg (19.5 in the Acute Phase and 27.5 in the Extension Phase). A total of 99 subjects were randomized to placebo. The percentages of randomized subjects in each treatment arm exposed to trial drug during the Acute Phase were: 100% (98 subjects) in the 10 mg arm, 100% (99 subjects) in the 30 mg arm, and 98% (97 subjects) in the placebo arm. The percentages of subjects in each treatment arm exposed to trial drug during the Extension Phase were: 76.5% (75/98 subjects) in the 10 mg arm, 71.7% (71/99 subjects) in the 30 mg-arm, and 64.6% (64/99 subjects) in the placebo arm.

Aripiprazole was generally safe and well tolerated by subjects in this trial. The majority of treatment-emergent adverse events (TEAEs) were mild or moderate in severity. No deaths were reported in this trial. There was 1 suicidal ideation event in each aripiprazole treatment arm, 10 mg and 30 mg, over the 30-week trial period, compared with no such events in the placebo arm.

The percentage of subjects who experienced at least one TEAE was slightly higher in the aripiprazole arms than in the placebo arm. During the Acute Phase, a total of 256 TEAEs were experienced by 72/98 (73.5%) subjects in the aripiprazole 10 mg arm; 326 TEAEs were experienced by 75/99 (75.8%) subjects in the aripiprazole 30 mg arm; and 156 TEAEs were experienced by 57/97 (58.8%) subjects in the placebo arm. During the entire trial period, a total of 376 TEAEs were experienced by 78/98 (79.6%) subjects in the aripiprazole 10 mg arm; 366 TEAEs were experienced by 84/99 (84.8%) subjects in the aripiprazole 30 mg arm; and 164 TEAEs were experienced by 64/97 (66.0%) subjects in the placebo arm.

During the Acute Phase, the most common TEAEs reported at an incidence rate of ≥ 5% in the aripiprazole 10 mg arm were somnolence (19.4%), headache (17.3%), fatigue (13.3%), extrapyramidal disorder (12.2%), nausea (9.2%), vision blurred (8.2%), vomiting (8.2%), akathisia (8.2%), decreased appetite (6.1%), and dizziness (5.1%). The most common TEAEs in the aripiprazole 30 mg arm were extrapyramidal disorder (27.3%), somnolence (26.3%), headache (19.2%), nausea (12.1%), akathisia (11.1%), fatigue (9.1%), vision blurred (8.1%), salivary hypersecretion (8.1%), vomiting (7.1%), increased appetite (5.1%), dizziness (5.1%), upper abdominal pain (5.1%), and dystonia (5.1%). In the placebo arm, the most common TEAEs were headache (16.5%), vomiting (9.3%), and bipolar disorder (5.2%).

During the 30-week trial, the most common TEAEs reported at an incidence rate of ≥ 5% in the aripiprazole 10 mg arm were somnolence (24.5%), headache (20.4%), fatigue (18.4%), nausea (13.3%), vomiting (13.3%), extrapyramidal disorder (12.2%), vision blurred (10.2%), nasal congestion (10.2%), upper abdominal pain (9.2%), akathisia (9.2%), increased weight (8.2%), increased appetite (8.2%), upper respiratory tract infection (8.2%), decreased appetite (7.1%), nasopharyngitis (7.1%), cough (7.1%), dizziness (7.1%), insomnia (6.1%), back pain (5.1%), anxiety (5.1%), dysmenorrhea (5.1%), and pharyngolaryngeal pain (5.1%). The most common TEAEs in the aripiprazole 30 mg arm were extrapyramidal disorder (28.3%), somnolence (27.3%), headache (23.2%), nausea (14.1%), akathisia (13.1%), fatigue (12.1%), vomiting (8.1%), vision blurred (8.1%), increased appetite (8.1%), salivary hypersecretion (8.1%), upper respiratory tract infection (6.1%), stomach discomfort (6.1%), bipolar disorder (6.1%), upper abdominal pain (5.1%), increased weight (5.1%), dizziness (5.1%), diarrhea (5.1%), and dystonia (5.1%). In the placebo arm, the most common TEAEs were headache (18.6%), vomiting (9.3%), bipolar disorder (5.2%), and nausea (5.2%).

During the Acute Phase, there appeared to be a general trend of increasing incidence across the treatment groups for the commonly reported TEAEs of nausea, salivary

hypersecretion, akathisia, extrapyramidal disorder, somnolence, dystonia, and headache, with the highest incidence in the aripiprazole 30 mg arm. In addition, a greater incidence of the following TEAEs was noted in the aripiprazole arms compared to the placebo arm: blurred vision, diarrhea, and dizziness. A similar TEAE profile was seen during the entire trial period (Acute + Extension Phases).

The percentages of subjects who experienced SAEs during the Acute Phase were: 5/98 (5.1%) and 2/99 (2.0%) in the aripiprazole 10 mg and 30 mg arms, respectively, and 5/97 (5.2%) in the placebo arm. The percentages of subjects who experienced SAEs at any time during the entire trial were: 5/98 (5.1%) and 7/99 (7.1%) in the aripiprazole 10 mg and 30 mg arms, respectively, and 6/97 (6.2%) in the placebo arm. The most commonly reported SAEs during the entire trial were bipolar disorder (9/294 subjects; 3.1% overall) and Bipolar I Disorder (3/294 subjects, 1.0% overall). During the Acute Phase, bipolar disorder was reported as serious in 2 subjects (2.0%) in the aripiprazole 30 mg arm and 4 subjects (4.1%) in the placebo arm. An additional 3 subjects in the aripiprazole 30 mg arm (for a total 5.1% in that group for the entire trial) had SAEs of bipolar disorder during the Extension Phase (ie, after Week 4 and before Week 30). An SAE of bipolar I disorder was reported in 2 subjects in the aripiprazole 30 mg arm during the Extension Phase (ie, after Week 4 and before Week 30), and 1 subject in the placebo arm during the Acute Phase.

The percentage of subjects who discontinued trial medication due to AEs was greatest in the aripiprazole 30 mg arm, particularly over the 30-week period. The percentages of subjects discontinued due to AEs during the Acute Phase were 6/98 (6.1%) and 8/99 (8.1%) in the aripiprazole 10 mg and 30 mg arms, respectively, and 2/97 (2.1%) in the placebo arm. The percentages of subjects discontinued due to AEs during the entire trial period were 9/98 (9.2%) and 19/99 (19.2%) in the aripiprazole 10 mg and 30 mg arms, respectively, and 2/97 (2.1%) in the placebo arm. The most commonly reported TEAEs resulting in discontinuation of trial medication (reported by more than 1 subject overall) during the Acute Phase were extrapyramidal disorder (3 subjects in the aripiprazole 30 mg arm), sedation (2 subjects in the aripiprazole 10 mg arm), fatigue (2 subjects in the aripiprazole 10 mg arm), and bipolar disorder (2 subjects in the aripiprazole 30 mg arm).

Extrapyramidal related side effects (EPS) [parkinsonism, akathisia, and dyskinesia] were evaluated with the SAS, BARS, and AIMS scales, respectively. Although some differences between the active and placebo groups reached statistical significance, these minimal changes were not considered clinically meaningful. The overall incidence of any extrapyramidal event reported as a TEAE was 25.8% (51/197 subjects) in the combined aripiprazole group and 5.1% (5/97 subjects) in the placebo group during the Acute Phase. There was no notable increase in extrapyramidal events following the Acute Phase (28.4% versus 5.1% for the entire 30-week period in the aripiprazole and placebo groups, respectively). The most commonly reported EPS-related symptoms were parkinsonism events (21.8% and 4.1% in the aripiprazole and placebo groups, respectively, during the Acute Phase). Akathisia events occurred in 10.1% (20/197 subjects) of the combined aripiprazole group and 2.0% (2/97 subjects) of the placebo

group during the Acute Phase. There was no notable increase in akathisia events following the Acute Phase (up to Week 30).

Overall, there were no apparent safety issues observed with the laboratory test, vital signs, or ECG results. No clinically relevant mean changes were observed in the insulin or fasting insulin results. Overall, no clinically meaningful trends were observed for any of the potentially clinically significant laboratory test abnormalities. Although several abnormalities in laboratory tests, vital signs, and ECG parameters were reported as TEAEs, all appeared to be isolated findings.

A mean decrease in prolactin levels relative to baseline was observed overall across all treatment groups. Mean decreases in prolactin levels relative to baseline were observed in the two aripiprazole treatment arms in male subjects, and in both of the aripiprazole arms and the placebo arm in female subjects. The mean changes from baseline to the last visit in prolactin levels were -2.58 ng/mL, -3.39 ng/mL, and 0.72 ng/mL in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms, respectively, in male subjects; and -5.39 ng/mL, -1.41 ng/mL, and -1.79 ng/mL, respectively, for female subjects. The incidence of low prolactin levels (less than or equal to 3 ng/dL in females and less than or equal to 2 ng/dL in males) during the Acute Phase was greatest in the aripiprazole 30 mg arm (35/89, 39.3%), followed by the aripiprazole 10 mg arm (22/87, 25.3%), and then by the placebo arm (2/85, 2.4%). During the entire trial period (Acute + Extension Phases), the overall incidence of low prolactin levels was greatest in the aripiprazole 30 mg arm (41/92, 44.6%), followed by the aripiprazole 10 mg arm (34/93, 36.6%), and then by the placebo arm (2/86, 2.3%).

The metabolic syndrome evaluation included assessment of the following tests: fasting blood levels for triglycerides, high density lipoprotein – cholesterol (HDL-C), and glucose; waist circumference; BMI; and supine and standing systolic and diastolic blood pressure. Overall, no clinically meaningful changes from baseline were observed in any of the metabolic syndrome evaluation parameters for males or females and no clinically meaningful trends were observed in the incidences of abnormalities for the metabolic syndrome parameters of fasting triglyceride levels, fasting HDL-C levels, fasting glucose levels, waist circumference, BMI, supine systolic or diastolic blood pressure, and standing systolic and diastolic blood pressure. The incidences of fasting cholesterol levels of $\geq$ 170 mg/dL were 39.3%, 48.1%, and 26.9% in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms, respectively, over the entire trial period; for the Acute Phase, the incidences were 40.5%, 43.1%, and 22.2%, respectively.

At the last visit, the percentages of subjects who experienced a potentially clinically significant weight gain ($\geq$ 7% weight gain compared to baseline) were 35.8% (34/95 subjects) in the aripiprazole 10 mg arm, 29.2% (28/96 subjects) in the aripiprazole 30 mg arm, and 9.8% (9/92 subjects) in the placebo arm. The differences from placebo in the incidence of potentially clinically significant weight gain were statistically significant at the last visit for both the aripiprazole 10 mg arm and 30 mg arm ($p < 0.0001$ and $p = 0.0009$, respectively). Overall, the mean weight and BMI z-scores for each visit

were within 0.5 SD of the population for all three treatment arms, and the changes from baseline were negligible. At the last visit, the mean change (SD) in weight z-score was 0.13 (0.35) with a range of −0.78 to 1.48 in the aripiprazole 10 mg arm; 0.17 (0.41) with a range of −1.09 to 2.20 in the aripiprazole 30 mg arm; and 0.01 (0.20) with a range of −0.49 to 0.73 in the placebo arm. At the last visit, the mean change (SD) in BMI z-score was 0.12 (0.41) with a range of −1.42 to 1.61 in the aripiprazole 10 mg arm; 0.19 (0.51) with a range of −1.05 to 2.79 in the aripiprazole 30 mg arm; and 0.01 (0.24) with a range of −0.59 to 1.06 in the placebo arm. Very few subjects had a shift in weight z-score from normal (< 95th percentile) at baseline to abnormal (weight z-score ≥ 95th percentile) at the last visit across all treatment groups.

Other Outcome Variables:

P-QLES-Q:

For the P-QLES-Q Total Score, improvements were observed in all three treatment arms using the LOCF data set, with numerically superior results in both aripiprazole arms versus placebo at Week 4; however, no statistically significant differences were observed.The P-QLES-Q Overall Scores showed no statistically significant differences between either aripiprazole treatment arm versus placebo at Week 4. However, at Week 30, a statistically significant improvement compared to placebo was seen in the aripiprazole 10 mg arm (0.3 versus −0.0, p = 0.0400) using the LOCF data set. The mean treatment effect was 0.35 (95% CI = 0.02 to 0.67) for the 10 mg arm.

Incidence of Hospitalizations:

The incidence of subjects hospitalized due to worsening of bipolar disorder was low, and there were no statistically significant differences in the incidence of hospitalization between treatment groups. No subjects required hospitalization due to worsening bipolar disorder among subjects who were insubjects at the beginning of the Acute Phase. Among subjects who were outsubjects at the beginning of the Acute Phase and insubjects at the end of the Acute Phase, 4 subjects required hospitalization due to worsening of bipolar disorder: 1/99 (1.0%) in the aripiprazole 30 mg arm and 3/99 (3.0%) in the placebo arm. Among subjects who were outsubjects at the beginning of the Acute Phase and outsubjects by the end of the Acute Phase, 1 subject in the placebo arm (1/99; 1.0%) required hospitalization due to worsening of bipolar disorder. For the entire trial (Acute + Extension Phases), no subjects required hospitalization due to worsening bipolar disorder among subjects who had been insubjects at the beginning of the trial. Among subjects who had been outsubjects at the beginning of the trial and insubjects by the end of the trial, a total of 5 subjects required hospitalization due to worsening of bipolar disorder: 2/99 (2.0%) in the aripiprazole 30 mg arm and 3/99 (3.0%) in the placebo arm. Among subjects who had been outsubjects at the beginning of the trial and outsubjects by the end of the trial, 3 subjects required outsubject hospitalization due to worsening of bipolar disorder: 1/99 (1.0%) in the aripiprazole 30 mg arm and 2/99 (2.0%) in the placebo arm. None of the subjects required more than one hospitalization.

Conclusions:

- Aripiprazole was effective for the treatment of child and adolescent subjects (ages 10 to 17 years) with bipolar I disorder, manic or mixed episode with or without psychotic features, at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared to placebo in the primary efficacy endpoint, mean change in YMRS Total Score at Week 4 (LOCF). Statistically significant improvements were seen as early as Week 1 for both doses and continued through Week 4 (LOCF).
- Aripiprazole doses of 10 mg and 30 mg were effective at Week 4 (LOCF) in the treatment of bipolar I disorder in children and adolescents (ages 10 to 17 years) in the following secondary endpoints: response rate (defined as ≥ 50% reduction of the baseline YMRS Total Score); and mean changes from baseline in CGAS score, CGI-BP Severity scores for Mania and Overall Bipolar Illness, respectively, CGI-BP change from preceding phase scores for Mania and Overall Bipolar Illness, respectively, GBI-Parent/Guardian Version and Subject Version Mania Total score, respectively, and the ADHD-RS-IV Total score.
- Efficacy was maintained through Week 30 (LOCF), with both aripiprazole doses showing a statistically significant sustained improvement over placebo for the efficacy endpoints: mean change from baseline in Y-MRS Total Score; response rate (defined as ≥ 50% reduction of the baseline YMRS Total Score); and mean changes from baseline in CGAS score, CGI-BP Severity scores for Mania and Overall Bipolar Illness, CGI-BP change from preceding phase score for Mania and Overall Bipolar Illness, GBI Parent Version Mania Total score, and ADHD-RS-IV Total score. The aripiprazole 30 mg dose also showed a statistically significant improvement over placebo for the GBI Subject Version Mania Total Score.
- Overall subject retention was high in the Acute Phase of this trial, with approximately 85.7%, 77.8%, and 76.8% completion rates in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively. No statistically significant differences were observed between treatment arms with respect to time to discontinuation due to all reasons in the Acute Phase.
- With regard to time to discontinuation for all reasons, both aripiprazole doses showed statistically significantly superior retention profiles over the 30-week trial (in Kaplan-Meier curves), ie, proportions of subjects remaining in the trial at different time points, compared to placebo.
- Aripiprazole was generally safe and well tolerated at daily doses of 10 mg and 30 mg in children and adolescents (ages 10 to 17 years) with bipolar I disorder. However, the 10 mg dose was better tolerated than the 30 mg dose based on the lower number of TEAEs and a lower incidence of EPS events in the 10 mg dose group.
- There was 1 suicidal ideation event in each aripiprazole treatment arm, 10 mg and 30 mg, over the 30-week trial period, compared with no such events in the placebo arm.
- Overall, 6 subjects experienced SAEs resulting in discontinuation of trial medication: in the aripiprazole 10 mg arm, 1 subject was discontinued due to suicidal ideation, and 1 subject was discontinued due to aggression and fatigue; in

the aripiprazole 30 mg arm, 3 subjects were discontinued due to bipolar disorder; and in the placebo arm, 1 subject was discontinued due to bipolar I disorder.

- The overall incidence of any extrapyramidal event was 25.8% (51/197 subjects) in the combined aripiprazole group and 5.1% (5/97 subjects) in the placebo group during the Acute Phase. The most commonly reported EPS-related symptoms were Parkinsonism events (21.8% and 4.1% in the aripiprazole and placebo groups, respectively, during the Acute Phase).
- Overall, there were no apparent safety issues observed with the laboratory test, vital sign, and ECG results.
- There appeared to be a mean decrease in prolactin levels relative to baseline across all treatment groups. The incidences of decreased serum prolactin (< 2 ng/mL for males; < 3 ng/mL for females) were 2%, 36% and 44%, respectively, in the placebo, 10 mg, and 30 mg dose groups at Week 30. A higher proportion of males experienced decreased prolactin levels than females in both dose groups. An overall low incidence (around 1%) of clinically significant hyperprolactinemia was observed in this trial.
- Overall, no clinically meaningful changes from baseline were observed in any of the metabolic syndrome evaluation parameters for males or females, and no clinically meaningful trends were observed in the incidences of abnormalities for the metabolic syndrome parameters of fasting triglyceride levels, fasting HDL-C levels, fasting glucose levels, waist circumference, BMI, supine systolic or diastolic blood pressure, and standing systolic and diastolic blood pressure. There were no clinically meaningful mean changes (> 0.5 SD) in weight z scores at the end of the trial (Last Visit). There was a low incidence of clinically significant weight gain (defined as ≥ 7% over baseline) observed at the end of the Acute Phase of 3.2%, 9.4%, and 3.3% for the aripiprazole 10 mg, 30 mg, and placebo groups, respectively. There was a greater incidence of weight gain at the end of the trial (Last Visit). The mean changes in weight at the end of the Acute Phase were 0.55, 0.90, and 0.54 kg for the aripiprazole 10 mg, 30 mg, and placebo arms, respectively. The mean changes in weight at the end of the trial (Last Visit) were 3.20, 2.85, and 0.98 kg for the aripiprazole 10 mg, 30 mg, and placebo arms, respectively. Very few subjects had a shift in weight z-score from normal (< 95th percentile) at Baseline to abnormal (weight z-score ≥ 95th percentile) at the Last Visit. Therefore, although weight changes occurred, they were not clinically relevant based upon z-scores and shift tables.
- Based on a comparison of the results of four adult clinical studies (CN138-007, CN138-008, CN138-009, and CN138-074) in bipolar disorder with the results of this pediatric bipolar disorder trial, some AEs (eg, somnolence, blurred vision, and extrapyramidal symptoms) appear to occur at a higher frequency in the pediatric population compared with the adult population with bipolar disorder. Both doses demonstrated a quality of life benefit in child and adolescent subjects based on improvements compared with placebo in both the P-QLES-Q Total and Overall Scores at Weeks 4 and 30 (LOCF).

- The incidence of hospitalization during the Acute Phase and for the entire 30-week trial period was similar across treatment arms, and the incidence of subjects hospitalized due to worsening of bipolar disorder was low.

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