Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597, BMS-337039)

Clinical Summary for Protocol 31-03-241
NCT No. 00102518

A Multi-center, Open-label, Safety and Tolerability Study of Flexible-dose Oral Aripiprazole (2 mg - 30 mg) in the Treatment of Adolescent Patients with Schizophrenia, and Child and Adolescent Patients with Bipolar I Disorder, Manic or Mixed Episode With or Without Psychotic Features (Protocol 31-03-241)

Indication:	Schizophrenia and Bipolar I Disorder
Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland, United States
Trial Initiation Date:	17 Sep 2004
Trial Completion Date:	26 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, BMS-337039)

Protocol Title: A Multi-center, Open-label, Safety and Tolerability Study of Flexible-dose Oral Aripiprazole (2 mg - 30 mg) in the Treatment of Adolescent Patients with Schizophrenia, and Child and Adolescent Patients with Bipolar I Disorder, Manic or Mixed Episode With or Without Psychotic Features (Protocol 31-03-241)

Trial Center(s) by Region: Multicenter (160 centers); Multinational (Argentina, Bulgaria, Croatia, India, Jamaica, Mexico, Romania, Russia, Serbia and Montenegro, South Africa, South Korea, Ukraine, and United States

Clinical Phase/Trial Type: Phase 3/Multicenter, open-label, flexible-dose trial

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: This safety and tolerability trial was part of the Aripiprazole Pediatric Efficacy Program (APEX) in response to the FDA's Written Request for Abilify™ and was designed to provide additional long-term safety and tolerability data on aripiprazole in adolescent subjects, ages 13 to 17 years, with schizophrenia, and in children and adolescent subjects, ages 10 to 17 years, with bipolar I disorder (manic or mixed episode, with or without psychotic features). Subjects who entered this trial rolled over from the APEX double-blind efficacy trials (the "parent trials"), OPDC Trial 31-03-239 (short-term treatment of subjects with schizophrenia) and Trial 31-03-240 (short-term treatment of subjects with bipolar I disorder acute manic or mixed episodes).

The dose range explored in this trial was 2 mg to 30 mg and was the same as dose range examined in the efficacy trials, referred to as the "parent trials," protocol numbers 31-03-239 and 31-03-240. Doses up to 30 mg have been well tolerated in adult subjects with schizophrenia, bipolar I disorder acute manic and mixed episodes, and maintenance treatment of these disorders.

Publications: None to date.

Objectives: The primary objective of the trial was to determine the long-term safety and tolerability of aripiprazole tablets (2 mg to 30 mg/day) in adolescent subjects with schizophrenia, and child and adolescent subjects with bipolar I disorder, manic or mixed episode with or without psychotic features.

Methodology: This was a multicenter, open-label, flexible dose trial to assess the long-term safety and tolerability of aripiprazole by enrolling subjects from the parent trials of the APEX. All subjects enrolled in Trial 31-03-241 had previously completed OPDC Trial 31-03-239 (adolescents with schizophrenia) or had withdrawn from the double-blind extension phase of OPDC Trial 31-03-240 (children and adolescents with bipolar I disorder).

Subjects enrolled were eligible to receive up to a total of 6 months of open-label aripiprazole treatment at daily doses of 2 mg to 30 mg. The open-label trial overlapped with the parent trial for 1 day. The End of Treatment/Early Termination evaluations conducted at the last office visit of the parent trial served as the baseline (Day 0) evaluation for the open-label trial, with the exception of the pharmacokinetic (PK) sampling, Clinical Global Impression Improvement (CGI-I) score and Children's Depression Rating Scale, Revised (CDRS-R) score. Informed consent and assent of the child and/or of his or her guardian were obtained and documented. This included assessments conducted to determine eligibility for participation in the open-label trial as well as any End of Treatment/Early Termination assessments conducted for the parent trial that were to be used as baseline assessments for the open-label trial.

On Day 0 of open-label treatment in Trial 31-03-241, subjects received an up-titration blister card which achieved the initial target dose of 10 mg on Day 5 preceded by aripiprazole 2 mg for 2 days (Days 1 and 2) and aripiprazole 5 mg for 2 days (Days 3 and 4). If the subject was unable to tolerate the titration during this fixed up-titration phase, the subject was withdrawn from the trial. On Day 7, the investigator had the option to continue the dose escalation up to a maximum of 30 mg/day, or, for tolerability issues, to reduce the dose of aripiprazole to no less than 5 mg/day for subjects with schizophrenia and to no less than 2 mg/day for subjects with bipolar I disorder. To escalate the dose, subjects received 15 mg for 2 days, 20 mg for 2 days, 25 mg for 2 days, and then 30 mg for 2 days as the highest dose. Dose escalation could stop at any dose level that the investigator felt was tolerable for the subject. Dose reduction, if necessary based on clinical judgment in regard to tolerability, occurred at a rate that was considered by the investigator to be appropriate for the subject.

Following the initial dose reduction, the investigator could escalate the subject's dose again based on clinical judgment at a rate that was considered by the investigator to be appropriate for the subject. Once a subject's dose had been escalated following the initial dose reduction, no further dose reductions were permitted. Failure to tolerate the medication after dose reduction to the minimal allowable dose level, or to the escalated dose level afterwards, resulted in removal of the subject from the trial.

This 6-month open-label safety trial was conducted on an outpatient basis with clinic visits at Weeks 1, 2, 3, 4, 8, 12, 18, and 26 (End of Treatment/Early Termination Visit.). However, limited inpatient hospitalization and/or more frequent evaluations were permitted at the investigator's discretion. In addition to the clinic visits, a follow-up phone call was to occur 30 days after the Week 26 Visit (at Week 30) to assess adverse events (AEs).

During the course of open-label treatment, psychotropic medications could be added with the exception of other antipsychotic agents. Prescriptions were to be made according to the respective drug label. However, over-the-counter medications were not to be used without approval from the medical monitor.

An independent Data Safety Monitoring Board (required by the United States Food and Drug Administration Pediatric Written Request) reviewed and evaluated cumulative safety data collected at regular intervals to ensure the safety of subjects enrolled in aripiprazole pediatric trials.

Number of Subjects: No predetermined sample size was calculated for the open-label trial because the trial population was derived from 2 parent trials (Trials 31 03 239 and 31-03-240). Three hundred twenty-five (325) subjects were screened for this trial and all 325 were enrolled in the trial.

Diagnosis and Main Criteria for Inclusion/Exclusion: Trial 31-03-241 enrolled adolescent subjects (13 to 17 years of age) with schizophrenia who had completed Trial 31-03-239 and children and adolescent subjects (10 to 17 years of age) with bipolar I disorder, manic or mixed episode, with or without psychotic features, who had withdrawn from the double-blind extension phase of Trial 31-03-240.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Aripiprazole was supplied as oral tablets in strengths of 2 mg, 5 mg, 10 mg, and 15 mg.
The dosing of aripiprazole (2 to 30 mg) was achieved using the following tablet combinations:
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 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: Not applicable.

Duration of Treatment: 26 weeks

Trial Assessments:
Safety assessments for all subjects:

- Extrapyramidal symptom scales (EPS): Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes-Akathisia Rating Scale (BARS);
- Vital signs (supine and standing positions), blood pressure, and electrocardiogram (ECG) parameters
- Serum prolactin concentrations, creatine phosphokinase (CPK), hemoglobin A1c, fasting insulin levels, triglycerides, high-density lipoproteins, fasting glucose, and routine laboratory tests

- Height, weight, body mass index (BMI) and waist circumference
- Adverse events, serious adverse events (SAEs) (clinical and laboratory), and discontinuation from the trial due to AEs.

Efficacy assessments for subjects with schizophrenia:
- Positive and Negative Syndrome Scale (PANSS) Total Score and the Positive and Negative subscales
- Clinical Global Impression Severity Scale (CGI-S) score and Clinical Global Impression Improvement Scale (CGI-I) score

Efficacy assessments for subjects with bipolar disorder:
- Young Mania Rating Scale score (Y-MRS)
- Clinical Global Impression Scale-Bipolar Version (CGI-BP) severity score
- General Behavior Inventory Scale (GBI) score
- Attention Deficit Hyperactive Disorders Rating Scale (ADHD-RS-IV) score

Efficacy assessments for all subjects
- Children's Depression Rating Scale-Revised (CDRS-R)
- Children's Global Assessment Scale (CGAS)

Other assessments for all subjects
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q)

Criteria for Evaluation:
Safety:
- Frequency and severity of AEs, SAEs (clinical and laboratory), and discontinuation from trial due to AEs
- Mean change from baseline by visit on the EPS symptom scales: SAS, AIMS, and BARS
- Mean change from baseline by visit in vital sign parameters (supine and standing positions), blood pressure, and ECG parameters
- Mean change from baseline by visit in serum prolactin concentrations, CPK, hemoglobin A1c, fasting insulin levels, triglycerides, high-density lipoproteins, and fasting glucose, and routine laboratory tests;
- Mean change from baseline by visit in BMI, waist circumference
- Percentage of subjects showing significant weight gain or loss from baseline (significant weight change was a ≥7% increase or decrease in weight);

Efficacy:
For subjects with schizophrenia, the following efficacy variables were evaluated by visit:

- Mean change from baseline on the (PANSS Total Score and on the Positive and Negative subscales; and
- Mean change from baseline on the (CGI-S) score and mean CGI-I score.

For subjects with bipolar I disorder (manic and mixed episode with or without psychotic features), the following efficacy variables were evaluated by visit:

- Mean change from baseline on the Y-MRS
- Mean change from baseline on the CGI-BP severity score
- Mean change from baseline on the GBI score
- Mean change from baseline on the ADHD-RS-IV) score

For all subjects, the following efficacy variables were evaluated by visit:

- Mean change from baseline on the CDRS-R
- Mean change from baseline on the CGAS)
- Time to discontinuation for all reasons

Other Variables:

- The P-QLES-Q at baseline (Day 0) and End of Treatment/Early Termination (Week 26).

Statistical Methods:

The core datasets for all analyses included all subjects (subpopulations of subjects with either schizophrenia, or bipolar I disorder

The baseline visit for this roll-over trial was defined as the last visit in the parent trials (31-03-239 and 31-03-240) in the protocol. However, the value at the last available scheduled visit with nonmissing values for each measure (except ECG) in the parent trials was used as baseline in the safety analysis in order to avoid missing baselines. The last scheduled nonmissing measurement at post-baseline for each subject was defined as the Last Visit measurement.

All demographic and routine safety variables were listed and, where appropriate, summarized using descriptive statistics (eg, proportion, mean, median, standard deviation[SD], minimum, and maximum). In particular, change from baseline at each visit for the continuous safety variables (eg, vital signs) was summarized using descriptive statistics.

The scheduled visits for EPS rating scales (SAS, AIMS, and BARS) were Weeks 1, 2, 3, 4, 8, 12, 18, and 26. A 3-day window was allowed for Weeks 1 to 4 and Week 8, and a 7-day window for Weeks 12, 18, and 26.

Potentially clinically significant abnormalities were listed by parent trial. Efficacy variables were summarized as changes from baseline and using descriptive statistics.

Subjects with missing baseline or post-baseline measurements were not included in the descriptive statistics for those variables or in the descriptive statistics for change from baseline to post-baseline. No missing data were imputed for vital signs, clinical laboratory tests, or ECG data.

The Observed Cases (OC) datasets were used for the EPS symptom rating scales derived for analysis by visit week. The OC dataset corresponding to a visit consisted of data from all subjects who were evaluated at that visit; subjects with missing data due to dropout or other reasons were not included in the OC dataset.

Summary of Results:

Baseline Data, Disposition, and Demographics:
In both subpopulations (ie, the subpopulation from Trial 31-03-239, adolescents with schizophrenia, and the subpopulation from Trial 31-03-240, children and adolescents with bipolar I disorder), the majority of subjects were male (55.6% of adolescent subjects with schizophrenia and 60.5% of children and adolescent subjects with bipolar I disorder) and non-Hispanic (85.4% of adolescent subjects with schizophrenia and 89.5% of children and adolescent subjects with bipolar I disorder).

Among the total combined subject population, 63.4% were Caucasian, 13.9% were "Other," 11.7% were black, 10.5% were Asian, 0.3% were American Indian or Alaskan Native, and 0.3% were Native Hawaiian or Other Pacific Islander. In the subpopulation of adolescent subjects with schizophrenia, 60.3% were Caucasian, 14.6% were identified as "Other," 14.2% were Asian, 10.5% were black, and 0.4% were American Indian or Alaskan native. In the subpopulation of children and adolescent subjects with bipolar I disorder, 72.1% were Caucasian, 15.1% were black, 11.6% were identified as "Other," and 1.2% were native Hawaiian or Pacific Islander.

The mean age was 15.7 years (range 13 to 18 years) in adolescent subjects with schizophrenia and 13.2 years (range 10 to 17 years) in children and adolescent subjects with bipolar I disorder.

A total of 325 subjects were enrolled and treated in this trial: 239/325 (73.5%) adolescent subjects with schizophrenia from Trial 31-03-239 and 86/325 (26.5%) children and adolescent subjects with bipolar I disorder from Trial 31-03-240. Overall, a total of 26.8% (87/325) of the subjects discontinued from the trial and the rates of discontinuation due AEs (2.2%) and lack of efficacy (2.2%) were low among subjects. Subject withdrawal of consent and loss to follow-up were the most common reasons for discontinuation. A total of 28/239 (11.7%) and 13/86 (15.1%) subjects withdrew consent and 7/239 (2.9%) and 8/86 (9.3%) subjects were lost to follow-up in the subpopulations of adolescent subjects with schizophrenia and children and adolescent subjects with bipolar I disorder, respectively.

Efficacy Results:

Overall, the greatest improvement in efficacy parameters was seen in the groups of subjects who had received placebo in their respective parent trials and were switched to aripiprazole in the current trial. Efficacy was maintained in the groups of subjects who had received aripiprazole 10 mg or 30 mg in their parent trial and continued to receive aripiprazole in the current trial. A summary of efficacy results at the Last Visit is shown below.

Mean Changes From Baseline (or Mean) in Efficacy Parameters at the Last Visit				
Sub-population, Parameter, Time point	**Treatment in Parent Study**			**Total**
	Aripiprazole 10 mg N Mean	**Aripiprazole 30 mg** N Mean	**Placebo** N Mean	**Aripiprazole** N Mean
Schizophrenia				
PANSS Total Score				
Baseline	80 62.16	77 62.58	77 72.26	234 65.62
Last Visit	80 -5.23	77 -6.21	77 -10.71	234 -7.35
CGI Severity Score				
Baseline	80 3.00	78 3.17	79 3.72	237 3.30
Last Visit	80 -0.38	78 -0.45	79 -0.70	237 -0.51
CGI Improvement Score (mean)				
Last Visit	80 2.26	78 2.38	79 2.53	237 2.39
PANSS Positive Subscale Score				
Baseline	80 13.41	77 14.35	77 16.73	234 14.81
Last Visit	80 -1.61	77 -1.87	77 -2.91	234 -2.12
PANSS Negative Subscale Score				
Baseline	80 17.43	77 17.31	77 19.94	234 18.21
Last Visit	80 -1.33	77 -1.70	77 -3.03	234 -2.01
Bipolar I Disorder				
Y-MRS Total Score				
Baseline	22 22.09	26 17.54	34 24.44	82 21.62
Last Visit	22 -6.09	26 -0.58	34 -14.29	82 -7.74
CGI-BP Mania Severity Score				
Baseline	22 3.36	27 2.74	36 4.08	85 3.47
Last Visit	22 -0.73	27 -0.07	36 -1.94	85 -1.04
CGI-BP Depression Severity Score				
Baseline	22 2.09	27 1.93	36 2.36	85 2.15
Last Visit	22 -0.55	27 0.19	36 -0.75	85 -0.40
CGI-BP Overall Bipolar Illness Severity Score				
Baseline	22 3.55	27 3.07	36 4.14	85 3.65
Last Visit	22 -0.82	27 -0.19	36 -1.83	85 -1.05

Mean Changes From Baseline (or Mean) in Efficacy Parameters at the Last Visit				
Sub-population, Parameter, Time point	**Treatment in Parent Study**			**Total**
	Aripiprazole 10 mg	**Aripiprazole 30 mg**	**Placebo**	**Aripiprazole**
	N Mean	**N Mean**	**N Mean**	**N Mean**
CGI-BP Mania Change from Preceding Phase				
Last Visit	22 2.23	27 2.96	36 1.92	85 2.33
CGI-BP Depression Change from Preceding Phase				
Last Visit	22 2.82	27 3.48	36 2.72	85 2.99
CGI-BP Overall Bipolar Illness Change from Preceding Phase				
Last Visit	22 2.23	27 3.15	36 2.11	85 2.47
GBI Total Mania Subject Version				
Baseline	22 9.77	25 7.80	36 10.61	83 9.54
Last Visit	22 -3.50	25 -0.64	36 -3.94	83 -2.83
GBI Total Mania Guardian Version				
Baseline	22 10.27	26 10.19	36 14.72	84 12.15
Last Visit	22 -3.77	26 -1.35	36 -6.72	84 -4.29
GBI Total Depression Subject Version				
Baseline	22 6.64	25 7.84	36 9.00	83 8.02
Last Visit	22 -1.82	25 -2.36	36 -2.39	83 -2.23
GBI Total Depression Guardian Version				
Baseline	22 8.45	26 8.27	36 10.50	84 9.27
Last Visit	22 -1.55	26 -0.54	36 -2.92	84 -1.82
ADHD-RS-IV Total Score				
Baseline	21 24.38	26 26.46	36 30.86	83 27.84
Last Visit	21 -5.86	26 -2.54	36 -12.31	83 -7.61
Both Populations				
CGAS				
Schizophrenia				
Baseline	80 63.90	77 61.77	77 55.14	234 60.32
Last Visit	80 6.86	77 6.97	77 8.90	234 7.57
Bipolar I Disorder				
Baseline	22 56.36	27 60.33	34 50.82	83 55.39
Last Visit	22 9.23	27 3.30	34 22.59	83 12.77
CDRS-R				
Schizophrenia				
Baseline	63 29.79	65 28.03	65 31.23	193 29.68
Last Visit	63 -1.62	65 -2.83	65 -5.49	193 -3.33
Bipolar I Disorder				
Baseline	22 31.32	25 32.24	29 29.72	76 31.01
Last Visit	22 -2.95	25 -0.88	29 -3.93	76 -2.64

Both subpopulations (adolescent subjects with schizophrenia and children and adolescent subjects with bipolar I disorder) had good overall retention rates during this trial, even though the subpopulation of children and adolescent subjects with bipolar I disorder had a higher discontinuation rate in the latter phase of the trial.

Safety Results: A total of 325 subjects were exposed to aripiprazole in this trial: 239 adolescent subjects with schizophrenia (who had completed Trial 31 03-239) at average daily doses ranging from 5.2 mg to 20.7 mg, and 86 children and adolescent subjects with bipolar I disorder (who had withdrawn from the double-blind extension phase of Trial 31-03-240) at average daily doses ranging from 4.9 mg to 17.7 mg. Of these 325 subjects, 165 (50.8%) were exposed to aripiprazole for ≥ 26 weeks and 232 subjects (71.4%) for > 20 weeks. This population represents a cumulative exposure to aripiprazole of 132 subject-years. Subjects overall received an average daily aripiprazole dose of 16.3 mg, ranging from 1.4 mg to 28.9 mg. The subjects treated for ≥ 26 weeks received an average daily dose of 16.8 mg.

Aripiprazole was generally safe and well tolerated by subjects in this trial. The majority of TEAEs were mild or moderate in severity. A total of 713 TEAEs were reported by 230 subjects: 165/239 (69.0%) of the subpopulation of adolescent subjects with and 65/86 (75.6%) of the subpopulation of children and adolescent subjects with bipolar I disorder.

The most common TEAEs reported at an incidence rate of ≥ 5% in the subpopulation of adolescent subjects with schizophrenia were extrapyramidal disorder (19.2%), somnolence (13.8%), insomnia (9.2%), akathisia (8.4%), weight increased (7.9%), headache (7.1%), nausea (6.7%), tremor (6.3%), vomiting (5.9%), nasopharyngitis (5.9%), and increased appetite (5.4%). In the subpopulation of children and adolescent subjects with bipolar I disorder, the most common TEAEs were headache (16.3%), nausea (10.5%), somnolence (10.5%), upper respiratory tract infection (8.1%), akathisia (8.1%), weight increased (7.0%), dizziness (7.0%), diarrhea (5.8%), irritability (5.8%), and nasal congestion (5.8%). Overall, EPS-related AEs were observed more commonly in the subpopulation of adolescent subjects with schizophrenia (63/239, 26.3%) than in the subpopulation of children and adolescent subjects with bipolar I disorder (6/86, 6.9%).

The percentages of subjects who experienced SAEs were similar between the subpopulation of subjects with schizophrenia (14/239, 5.9%) and the subpopulation of children and adolescent subjects with bipolar I disorder (6/86, 7.0%). One subject (0.3%) in the adolescent population with schizophrenia experienced suicidal ideation. One death, an accidental electrocution, which was not attributed to trial drug by the investigator, was reported in this trial in the subpopulation of adolescents with schizophrenia.

The percentages of subjects who discontinued trial medication due to AEs were similar between the subpopulation of subjects with schizophrenia (6/239, 2.5%) and the subpopulation of children and adolescent subjects with bipolar I disorder (1/86, 1.2%). EPS-related side effects (parkinsonism, akathisia, and dyskinesia) were evaluated with the SAS, BARS, and AIMS scales, respectively. The minimal overall mean changes observed in this trial were not considered clinically meaningful.

No clinically relevant transaminase elevations or changes in hematology parameters were noted during long-term treatment with aripiprazole in the subpopulation of adolescents with schizophrenia. The incidence of potentially clinically significant clinical chemistry values was≥ 2% for all parameters tested except for CPK (5.2%), eosinophils (4.3%) and prolactin (3.0%). No clinically relevant transaminase elevations or changes in hematology parameters were noted during long-term treatment with aripiprazole in the subpopulation of children and adolescents with bipolar I disorder. The incidence of potentially clinically significant clinical chemistry values was ≥ 2% for all parameters tested except for CPK (6.0%).

No clinically meaningful changes in mean QT or QTc intervals, or other ECG abnormalities, were observed in the subpopulation of adolescent subjects with schizophrenia or in the subpopulation of children and adolescent subjects with bipolar I disorder following long-term treatment with aripiprazole.

Overall, there was a low incidence of clinically significant orthostatic hypotension (6/323, 1.9%), defined as a ≥ 20 mmHg decrease in systolic blood pressure accompanied by a 25 bpm increase in heart rate when moving from the supine to the standing position: 1/237 (0.4%) in the subpopulation of adolescent subjects with schizophrenia and 5/86 (5.8%) in the subpopulation of children and adolescents with bipolar I disorder.

A small mean decrease in prolactin levels relative to baseline was observed overall in both subpopulations. The decreases in prolactin levels were smaller in females than for males in both subpopulations. The overall incidence of low prolactin levels (< 3 ng/dL in females and < 2 ng/dL in males) was greater in the subpopulation of children and adolescents with bipolar I disorder than in the subpopulation of adolescents with schizophrenia (38/83 [45.8%] and 80/230 [34.8%], respectively). When analyzed by sex, similar results were observed for males, ie, more males in the subpopulation of children and adolescents with bipolar I disorder had low prolactin levels than did males in the subpopulation of adolescents with schizophrenia. For males, the incidence of low prolactin levels was 55/126 (43.7%) in the subpopulation of adolescent subjects with schizophrenia and 29/49 (59.2%) in the subpopulation of children and adolescent subjects with bipolar I disorder. For females, the incidence of low prolactin levels was 25/104 (24.0%) in the subpopulation of adolescent subjects with schizophrenia and 9/34 (26.5%) in the subpopulation of children and adolescent subjects with bipolar I disorder. None of these events were reported as TEAEs or SAEs or resulted in discontinuation of trial medication.

At the Last Visit, the percentage of subjects who experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline) was greater in the subpopulation of children and adolescent subjects with bipolar I disorder (38/86, 44.2%) than in the subpopulation of adolescent subjects with schizophrenia (58/237, 24.5%). The percentage of subjects who experienced a potentially clinically significant weight loss (≥ 7% weight loss compared to baseline) at the Last Visit was 11/237 (4.6%) in the subpopulation of adolescent subjects with schizophrenia and 1/86 (1.2%) in the

subpopulation of children and adolescent subjects with bipolar I disorder. However, overall, the mean changes from baseline for weight and BMI z-scores for each visit were within 0.5 SD of the general population for both subpopulations, which is considered within normal limits for this population, and the changes from baseline were negligible. At the Last Visit, the mean change (SD) in weight z-score was 0.05 (0.44), with a range of −1.17 to 1.73 in the subpopulation of adolescent subjects with schizophrenia, and 0.12 (0.29), with a range of −1.63 to 0.60 in the subpopulation of children and adolescent subjects with bipolar I disorder. At the Last Visit, the mean (SD) BMI z-score was 0.03 (0.52), with a range of −1.80 to 2.14 in the subpopulation of adolescent subjects with schizophrenia, and 0.12 (0.38), with a range of −1.60 to 1.86 in the subpopulation of children and adolescent subjects with bipolar I disorder. Similar results were observed for the mean change from baseline in BMI z-scores for males and for females.

Other Outcome Variables: Overall, subjects in both subpopulations showed similar improvements in P-QLES-Q Total Scores and P-QLES-Q Overall Scores at the Last Visit (1.73 and 0.04, respectively, in the subpopulation of children and adolescent subjects with bipolar I disorder and 1.16 and 0.02, respectively, the subpopulation of adolescent subjects with schizophrenia).

Conclusions:

- Long-term safety data were available from 325 child and adolescent subjects with schizophrenia or bipolar mania (mean age of 15 years), who rolled over from parent double-blind trials 31-03-239 or 31-03-240 to receive oral aripiprazole for up to 6 months. Of these 325 subjects, 165 (50.8%) were exposed to aripiprazole for ≥ 26 weeks and 232 (71.4%) for > 20 weeks. This population represents a cumulative exposure to aripiprazole of 132 subject-years.
- Subjects overall received an average daily aripiprazole dose of 16.3 mg, ranging from 1.4 mg to 28.9 mg. The subjects treated for ≥ 26 weeks received an average daily dose of 16.8 mg.
- A total of 26.8% of the subjects discontinued from the trial and the rates of discontinuation due to adverse events (2.2%) and lack of efficacy (2.2%) were low among subjects.
- Aripiprazole was effective in the long-term, open-label treatment of adolescent subjects with schizophrenia when administered at daily doses ranging from 5 to 30 mg. In the subpopulation of adolescent subjects with schizophrenia, the evaluation of efficacy was based on mean change from baseline on the PANSS Total Score, Positive and Negative subscales, and CGI-S, as well as the mean CGI-I scores.
- Aripiprazole was effective in the long-term, open-label treatment of children and adolescent subjects with bipolar I disorder when administered at daily doses ranging from 2 to 30 mg. In the subpopulation of children and adolescent subjects with bipolar I disorder, the evaluation of efficacy was based on mean change from baseline on the Y-MRS, CGI-BP Severity Score (mania, depression, overall illness), GBI scale score (Subject and Guardian version for mania and depression), and the ADHD-RSIV

Total score, as well as the change from the preceding phase score in CGI-BP (mania, depression, overall illness).

- Overall, the greatest improvement in efficacy parameters in both subpopulations was seen in the groups of subjects who had received placebo in their respective parent trials and were switched to aripiprazole in the current trial. However, efficacy was maintained in the groups of subjects who had received aripiprazole 10 mg or 30 mg in their parent trial and continued to receive aripiprazole in the current trial. These results confirm the efficacy results seen in the parent trials (31-03-239 and 31-03-240).
- Aripiprazole was generally safe and well tolerated at average daily doses ranging from 5.2 mg to 20.7 mg in adolescents with schizophrenia, with the majority of TEAEs reported as mild or moderate. The incidences of serious TEAEs (5.9%) and discontinuation due to AEs (2.5%) were low. The most common TEAEs (≥ 5% of subjects), irrespective of causality, were extrapyramidal disorder (19.2%), somnolence (13.8%), insomnia (9.2%), akathisia (8.4%), increased weight (7.9%), headache (7.1%), nausea (6.7%), tremor (6.3%), nasopharyngitis (5.9%), vomiting (5.9%), and increased appetite (5.4%). One death was reported in this trial in the subpopulation of adolescents with schizophrenia. This death was an accidental electrocution and was not related to trial drug.
- Aripiprazole was also generally safe and well tolerated at average daily doses ranging from 4.9 mg to 17.7 mg in children and adolescents with bipolar I disorder, with the majority of TEAEs reported as mild or moderate. The incidences of serious TEAEs (7.0%) and discontinuation due to AEs (1.2%) were low. The most common TEAEs (≥ 5% of subjects), irrespective of causality, were headache (16.3%), nausea (10.5%), somnolence (9.5%), akathisia (8.1%), upper respiratory tract infection (8.1%), dizziness (7.0%) increased weight (7.0%), diarrhea (5.8%), irritability (5.8%), and nasal congestion (5.8%).
- Overall, EPS-related AEs were observed more commonly in the subpopulation of adolescent subjects with schizophrenia (63/239, 26.3%) than in the subpopulation of children and adolescent subjects with bipolar I disorder (6/86, 6.9%).
- Only 1 (0.3%) case of suicide ideation was reported during long-term administration of aripiprazole to adolescents with schizophrenia. There were no cases of suicide ideation reported during long-term administration of aripiprazole to children and adolescents with bipolar I disorder.
- No clinically relevant transaminase elevations or changes in hematology parameters were noted during long-term treatment with aripiprazole in the subpopulation of adolescents with schizophrenia. The incidence of potentially clinically significant clinical chemistry values was ≥2% for all parameters tested except for CPK (5.2%), eosinophils (4.3%) and prolactin (3.0%). No clinically relevant transaminase elevations or changes in hematology parameters were noted during long-term treatment with aripiprazole in the subpopulation of children and adolescents with bipolar I disorder. The incidence of potentially clinically significant clinical chemistry values was ≥2% for all parameters tested except for CPK (6.0%).

- In the subpopulation of adolescent subjects with schizophrenia, decreased serum prolactin (< 2 ng/mL for males; < 3 ng/mL for females) occurred in 34.8% of subjects, with a higher proportion of males experiencing a decrease relative to females (43.7% versus 24.0%). In the subpopulation of children and adolescent subjects with bipolar mania, decreased serum prolactin (< 2 ng/mL for males; < 3 ng/mL for females) occurred in 45.8% of subjects, with a higher proportion of males experiencing a decrease relative to females (59.2% versus 26.5%). The clinical relevance of these findings is unknown in the pediatric population.
- No clinically meaningful changes in mean QT or QTc intervals, or other ECG abnormalities, were observed in the subpopulation of adolescent subjects with schizophrenia or in the subpopulation of children and adolescent subjects with bipolar I disorder following long-term treatment with aripiprazole.
- Overall, there was a low incidence of clinically significant orthostatic hypotension (6/323, 1.9%), defined as a ≥ 20 mmHg decrease in systolic blood pressure accompanied by a 25 bpm increase in heart rate when moving from the supine to the standing position: 1/237 (0.4%) in the subpopulation of adolescent subjects with schizophrenia and 5/86 (5.8%) in the subpopulation of children and adolescents with bipolar I disorder.
- In the subpopulation of adolescent subject with schizophrenia, at the Last Visit, the percentage of subjects who experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline) was 24.5%; 4.6% of subjects experienced a weight loss of ≥ 7% relative to baseline. In the subpopulation of children and adolescent subject with bipolar I disorder, at the Last Visit, the percentage of subjects who experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline) was 44.2%; 1.2% of subjects experienced a weight loss of ≥ 7% relative to baseline. Overall, the mean changes from baseline for weight and BMI z-scores for the Last Visit were within 0.5 SD of the general population for both subpopulations, and the changes from baseline were negligible.

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