Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597, BMS-337039)

**Clinical Summary for Protocol 31-03-239**
**NCT No. 00102063**

# A Multicenter, Randomized, Double-blind, Placebo-controlled Study of Two Fixed Oral Doses of Aripiprazole (10 mg or 30 mg) in the Treatment of Adolescent Patients with Schizophrenia

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| Indication: | Schizophrenia |
| Clinical Development Phase: | 3 |
| Sponsor: | Otsuka Pharmaceutical Development & Commercialization, Inc.<br>2440 Research Boulevard<br>Rockville, MD, USA |
| Trial Initiation Date: | 02 Aug 2004 |
| Trial Completion Date: | 21 Aug 2006 |
| 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 Multicenter, Randomized, Double-blind, Placebo-controlled Study of Two Fixed Oral Doses of Aripiprazole (10 mg or 30 mg) in the Treatment of Adolescent Patients with Schizophrenia

**Trial Center(s) by Region:** Of 141 centers initiated, 115 centers screened subjects and, of these centers, 101 randomized subjects (Argentina [7 centers screened/ 6 centers randomized], Bulgaria [5/5], Croatia [5/4], India [11/10], Jamaica [1/1], Mexico [4/3], Romania [2/2], Russia [12/12], Serbia [3/3], South Africa [2/2], South Korea [3/3], Ukraine [6/6], and United States of America [54/44]).

**Clinical Phase/Trial Type:** 3/Multicenter, Randomized, Double-blind, Placebo-controlled

**Trial Interruption:** There was no unplanned trial interruption.

**Scientific Background and Explanation of Rationale:** This fixed dose trial was designed to test the safety and efficacy of oral aripiprazole tablets 10 mg once daily (QD) and 30 mg QD compared to placebo in adolescent subjects with Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) schizophrenia. This trial was conducted in response to the United States Food and Drug Administration's (FDA's) Pediatric Written Request (PWR) to systematically study the safety and efficacy of aripiprazole in adolescents with a primary diagnosis of schizophrenia.

While the diagnostic criteria for DSM-IV schizophrenia are the same in the pediatric and adult populations, the prevalence and symptoms of schizophrenia differ. Generally, the diagnosis of childhood schizophrenia is more difficult to determine than adult schizophrenia because of different presenting symptoms.[1, 2] Schizophrenia is less commonly diagnosed in younger children,[3] with one estimate suggesting that only about 0.1 to 1% of schizophrenic psychoses present before the age of 10.[4] The diagnosis in the pediatric population is typically made during the adolescent years when the symptoms are more similar to those in adults.[5] For these reasons, the population evaluated in this trial was limited to subjects between the ages of 13 and 17 years.

Aripiprazole doses of up to 30 mg have been well tolerated in adult subjects with schizophrenia, acute manic and mixed episodes associated with bipolar disorder, and the maintenance treatment of these disorders. In the pediatric population, aripiprazole doses up to 15 mg had been studied in a pharmacokinetic (PK) trial,[6] and doses of up to 30 mg had been widely prescribed in the postmarketing setting. The postmarketing data from 19 November 2002 to 9 January 2005 revealed that the pattern of adverse event (AE) frequency seen in pediatric subjects, 2.5 to 17 years of age, who received aripiprazole in a dosing range of 3.5 mg QD to 30 mg QD was similar to that observed in the adult population, thus, it did not deviate significantly from the known safety profile of aripiprazole.

Pharmacokinetic results indicated the total apparent oral clearance of drug (CLT/F) of aripiprazole was approximately 34% lower in children compared to adolescents and adults and was reasonably similar between adolescents and adults. When normalized for body weight, the values for the mean CLT/F were consistent across children, adolescents, and adults.[6]

Given these considerations, it was determined to be safe to test doses up to 30 mg QD in adolescent subjects with schizophrenia in this trial.

**Publications:**

Robb AS, Carson WH, Nyilas M, Ali M, Forbes RA, Iwamoto T, Assunção-Talbott S, Whitehead R, Pikalov A. Changes in positive and negative syndrome scale-derived hostility factor in adolescents with schizophrenia treated with aripiprazole: post hoc analysis of randomized clinical trial data. J Child Adolesc Psychopharmacol. 2010 Feb;20(1):33-8.

Findling RL, Robb A, Nyilas M, Forbes RA, Jin N, Ivanova S, Marcus R, McQuade RD, Iwamoto T, Carson WH. A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. Am J Psychiatry. 2008 Nov;165(11):1432-41.

**Objectives:** The primary objective of this trial was to determine the safety and efficacy of aripiprazole tablets administered as 10 mg QD and 30 mg QD in adolescent subjects, 13 to 17 years of age, with a DSM-IV diagnosis of schizophrenia. This trial was designed in response to the FDA's PWR.

**Methodology:** This trial was a multicenter, randomized, double-blind, placebo controlled trial designed to assess the safety and efficacy of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in adolescent subjects, 13 to 17 years of age (inclusive), with a DSM-IV diagnosis of schizophrenia. The DSM-IV diagnosis was confirmed by administering the Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version (K-SADS-PL) semi-structured interview of patients and parents/caregivers by an adequately trained clinician. Confirmation of the DSM-IV diagnosis of schizophrenia using a valid and reliable semi-structured interview was required in the PWR.The trial was conducted on an outpatient basis (with the option for inpatient hospitalization, if needed), and in a partial or full inpatient setting at any given time in the trial. Due to a regulatory authority request in Argentina, subjects were required to be hospitalized for the first 2 weeks of the trial, with extended hospitalization if needed. Subjects participated in this trial for up to 10 weeks, including a 28-day screening period, and a 42-day treatment period. Eligible subjects who completed this trial had the option to enroll into an open-label safety trial of aripiprazole (Trial 31-03-241) for an additional 6 months. For any subject who did not roll over into the open-label trial, 31-03-241, a follow-up telephone call was made 30 days after the last dose of trial medication to assess for any AEs.

After a minimum 3-day antipsychotic washout period, only subjects who continued to meet entrance criteria (Positive and Negative Syndrome Scale [PANSS] Total Score ≥70) at the baseline visit (Day 1) were evenly randomized to receive a double-blind medication as follows:

- Arm 1 (10 mg treatment arm): Aripiprazole 2 mg QD for 2 days, aripiprazole 5 mg QD for 2 days, and aripiprazole 10 mg QD as the target dose, starting on Day 5.
- Arm 2 (30 mg treatment arm): Aripiprazole 2 mg QD for 2 days, aripiprazole 5 mg QD for 2 days, aripiprazole 10 mg QD for 2 days, aripiprazole 15 mg QD for 2 days, aripiprazole 20 mg QD for 2 days, and aripiprazole 30 mg QD as the target dose, starting on Day 11.
- Arm 3 (placebo arm): Matching placebo for aripiprazole tablets.

Aripiprazole was titrated to the target dose in 5 days in the 10 mg treatment arm and in 11 days in the 30 mg treatment arm. Subjects remained at the assigned dose for at least 2 weeks. Subjects who experienced dose-related tolerability issues prior to trial Day 25 were to be discontinued from the trial. Beginning on Day 26, investigators could decrease the dose of aripiprazole for tolerability (to 5 mg QD in the 10 mg treatment arm and to 15 mg QD in the 30 mg treatment arm).

Mandatory subject evaluations were performed at Days 1 (baseline), 7, 14, 21, 28, 35, and 42/early termination (ET). A telephone assessment was performed at Day 4 to inquire about AEs and compliance with dosing. More frequent evaluations were permitted at the discretion of the investigator.

If subjects were not able to tolerate the assigned dose or the decreased dose, or had no improvement in schizophrenia symptoms, they were to be discontinued from the double-blind trial. Per the FDA's PWR, the trial allowed for early rescue, ie, treatment with a compassionate medication, in the event of discontinuation. Reimbursement for a compassionate medication supplement for up to 12 weeks was offered to these subjects.

An independent data safety monitoring board (DSMB) (required by the PWR) reviewed and evaluated cumulative safety data collected at regular intervals to ensure the safety of subjects enrolled in aripiprazole pediatric trials.

**Number of Subjects:** As specified in the PWR, this trial was designed to have 85% power to show a difference between aripiprazole and placebo equivalent to the median of the mean differences seen in the adult aripiprazole studies for schizophrenia. To have sufficient power, a minimum of 350 subjects at 141 sites globally were anticipated to be screened with the expectation that approximately 300 subjects would be randomized to yield at least 255 evaluable subjects (85 per treatment arm). A total of 302 subjects were randomized, 100 to aripiprazole 10 mg, 102 to aripiprazole 30 mg, and 100 to placebo.

Of these, 93/302 (30.8%) were randomized in the US, 141/302 (46.7%) were randomized in Europe, and 68/302 (22.5%) were randomized in other regions.

**Diagnosis and Main Criteria for Inclusion/Exclusion:** Male and female subjects, 13 to 17 years of age, with a K-SADS-PL confirmed Axis I (DSM-IV) diagnosis of schizophrenia, who had a PANSS Total Score ≥70 at baseline (Day 1). Subjects diagnosed with schizoaffective disorder, major depressive disorder, delirium, or bipolar disorder were excluded.

**Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration:** Aripiprazole oral tablets and matching placebo as follows: aripiprazole 2-mg tablets, dosed 2 mg QD; aripiprazole 5-mg tablets, dosed 5 mg QD; aripiprazole 10-mg tablets, dosed 10 mg QD; aripiprazole 10-mg and 5-mg tablets, dosed 15 mg QD; aripiprazole 10-mg tablets, dosed 20 mg QD; aripiprazole 15-mg tablets, dosed 30 mg QD; and matching placebo tablets.

**Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration:** Not applicable.

**Duration of Treatment:** 42 days.

**Trial Assessments:**
*Efficacy:* PANSS, Children's Global Assessment Scale (CGAS), Clinical Global Impression (CGI)-Severity Scale, CGI-Improvement Scale, and time to discontinuation due to all reasons.

*Pharmacokinetics:* Plasma aripiprazole and dehydro-aripiprazole metabolite concentrations.

*Safety*: AEs, vital signs, electrocardiogram (ECG), routine laboratory tests, physical examination findings, Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes-Akathisia Rating Scale (BARS), weight, body mass index (BMI), waist circumference, blood pressure (BP), and fasting insulin levels, triglycerides, high density lipoprotein cholesterol (HDL-C), glucose, and concomitant medications.

*Other Outcome Measures*: The number of hospitalizations for each subject and the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q).

**Criteria for Evaluation:**
*Primary Efficacy Variable*: The primary efficacy measure was the mean change from Baseline to Endpoint (Day 42) in the PANSS Total Score.

*Secondary Efficacy Variables*: Secondary efficacy measures were the mean changes in scores from Baseline to Endpoint (Day 42) in the CGAS, CGI-Severity Scale,

CGI-Improvement Scale, and PANSS Positive and PANSS Negative Subscales; and time to discontinuation due to all reasons.

*Pharmacokinetic Variables*: Plasma aripiprazole and dehydro-aripiprazole concentrations were measured in plasma samples for a population PK analysis to be reported separately.

*Safety Variables*: The primary safety measures were as follow:

- The frequency and severity of AEs, serious adverse events (SAEs) (clinical and laboratory), and discontinuation from trial due to AEs
- Mean change from Baseline to Endpoint (Day 42) in vital signs (supine and standing positions), ECG, routine laboratory tests (including fasting insulin levels, serum prolactin concentrations, and creatine phosphokinase [CPK]),and by-subject assessment of physical examination findings
- Mean change from Baseline to Endpoint (Day 42) on the SAS, AIMS, and BARS
- Percentage of subjects showing significant weight gain or loss from randomization to Day 42 (significant weight change was defined as ≥7 % increase or decrease in weight)
- Change from Baseline to Endpoint (Day 42) in BMI, waist circumference, BP, and fasting insulin levels, triglycerides, HDL-C, and glucose

For the purpose of this report, BMI, waist circumference, systolic and diastolic BP, and fasting triglycerides, HDL-C, and glucose were evaluated as part of the metabolic syndrome evaluation.

*Other Outcome Measures*: The number of hospitalizations for each subject was collected and the P-QLES-Q was administered (in translated languages where available) at screening and Day 42.

**Pharmacokinetic/pharmacodynamic Methods:** Blood samples were obtained on Days 1, 7, 14, 21, 28, 35, and 42/ET. A single 4-mL sample was obtained at predose on Day 1 and at any time during the other visits. Plasma concentrations of aripiprazole and dehydro-aripiprazole were simultaneously measured by a validated high-performance liquid chromatography method with tandem mass spectrophotometric detection. The concentration data will be used for population PK analyses, to be reported separately.

**Statistical Methods:**

*Primary Efficacy Analysis*: The primary efficacy endpoint was the change from baseline in PANSS Total Score at Day 42 (Week 6) in the last observation carried forward (LOCF) data set. The primary statistical comparisons were aripiprazole 10-mg target

dose versus placebo, and aripiprazole 30-mg target dose versus placebo. All randomized subjects who had both baseline and postbaseline PANSS Total Scores were included in the primary efficacy analysis.

Descriptive statistics for PANSS Total Scores and change from baseline scores were presented by treatment group for each visit. The change from baseline scores (LOCF) were analyzed using an analysis of covariance (ANCOVA) model with treatment and region as factors, and baseline PANSS Total Score as covariate. The treatment by region interaction term was investigated. For the baseline PANSS Total Score, only treatment and region were included in the analysis of variance (ANOVA) model. The least squares (LS) means obtained from the type III analysis using Statistical Analysis System were used for the treatment comparisons. Two-tailed student's t-tests were used to test the difference between LS means within the ANCOVA or ANOVA model.

A nominal overall significance level of 0.05 (two-tailed) was used in testing statistical significance of these two comparisons. In order to account for multiplicity in testing the two comparisons, the following Hochberg's procedure was used: if both p-values were less than 0.05 (two-tailed), statistical significance was declared for both doses. If the larger of the two p-values was greater than 0.05, the smaller p-value was compared with 0.025 (two-tailed) and the corresponding treatment comparison was declared statistically significant if this p-value was less than 0.025.

*Secondary Efficacy Analysis*: In addition to the primary analysis of the PANSS Total Score at Week 6, analyses of changes from baseline in PANSS Total Scores were performed as secondary analyses at all scheduled visits for both LOCF and observed cases (OC) data sets. Additional secondary efficacy variables were as follows: 1) changes from baseline score in CGAS score; 2) changes from baseline score in CGI−Severity Score; 3) CGI-Improvement Score; 4) changes from baseline in PANSS Positive Subscale Score; 5) changes from baseline in PANSS Negative Subscale Score; and 6) time to discontinuation due to all reasons.

Variables 1, 2, 4, and 5 were analyzed similarly to the primary efficacy analysis (PANSS Total Score) for Weeks 1 through 6 by fitting an ANCOVA model with treatment and region as factors, and baseline score as covariate. At baseline, these variables were analyzed using an ANOVA model with treatment and region as factors. Variable 3 was analyzed for Weeks 1 through 6 using the Cochran-Mantel-Haenszel (CMH) method stratified by region based on raw mean score statistics. Variable 6 was analyzed by plotting the Kaplan-Meier curves and testing for significance of the differences in survival curves using the log-rank test. The statistical comparisons were performed for aripiprazole 10-mg target dose versus placebo and aripiprazole 30-mg target dose versus placebo.

*Pharmacokinetics*: No statistical analysis of pharmacokinetic data was planned or conducted for this trial.

*Safety*: The safety variables were categorized into 4 groups: routine safety assessments (AEs, physical examination and vital signs, ECGs, and clinical laboratory evaluations); extrapyramidal symptom (EPS) rating scales (SAS, BARS, and AIMS), metabolic syndrome evaluation (waist circumference, BMI, diastolic and systolic BP, and fasting serum triglycerides, HDL-C, and glucose levels), and other safety data. All routine safety variables were listed and, where appropriate, summarized by descriptive statistics. In particular, change from baseline at each visit for the continuous safety variables was summarized using descriptive statistics. However, no inferential statistical analyses of these safety variables were performed. For EPS safety variables, the changes from baseline in SAS Total Score, BARS Global Score, and AIMS Movement Rating Score over items 1 to 7 were analyzed by ANCOVA with treatment group and region as factors and baseline as covariates except that at baseline only treatment and region were included in the ANOVA model. Incidences of metabolic syndrome abnormalities were summarized by treatment group at each visit. Similar tables were provided by gender. Descriptive statistics for original values and changes from baseline were summarized for scheduled visit and last visit by treatment group. Additionally, potentially clinically significant changes in weight were summarized by visit, and mean changes from baseline in weight and BMI z-scores were provided.

*Other Outcome Measures*: Other outcome measures were: 1) changes from baseline in P-QLES-Q Total Score; 2) changes from baseline in the P-QLES-Q Overall Score; and 3) proportion of subjects hospitalized due to worsening of schizophrenia.

Variable 1 was analyzed by fitting the ANCOVA model with treatment and region strata as factors, and/or baseline value as covariate. Variable 2 was a discrete score. It was analyzed by using the CMH raw mean score statistics stratified by region. Variable 3 was summarized by treatment group hospitalization status prior to randomization and at trial completion/discontinuation, and reasons for hospitalization due to the AEs of worsening of schizophrenia and other causes resulting in hospitalization.

**Summary of Results:**

**Baseline Data, Disposition, and Demographics:** A total of 302 subjects were randomized and treated in this trial: 100/302 (33.1%) in the aripiprazole 10-mg arm, 102/302 (33.8%) in the aripiprazole 30-mg arm, and 100/302 (33.1%) in the placebo arm. Of these, 93/302 (30.8%) were randomized in the US, 141/302 (46.7%) were randomized in Europe, and 68/302 (22.5%) were randomized in other regions. All randomized subjects were included in the efficacy and safety analyses.

Subjects who completed the Day 42 visit were defined as completers. A total of 258/302 (85.4%) subjects completed the trial: 84/100 (84.0%) in the aripiprazole 10-mg arm, 84/102 (82.4%) in the aripiprazole 30-mg arm, and 90/100 (90.0%) in the placebo arm.

A high rate of retention was observed in this trial. A total of 264/302 (87.4%) subjects completed 36 days or more: 87/100 (87.0%) in the aripiprazole 10-mg arm, 85/102 (83.3%) in the aripiprazole 30-mg arm, and 92/100 (92.0%) in the placebo arm.

Overall, AEs and subject withdrawal of consent were the most common reasons for discontinuation. A total of 7/100 (7.0%), 4/102 (3.9%), and 2/100 (2.0%) subjects withdrew due to AEs and 4/100 (4.0%), 12/102 (11.8%), and 5/100 (5.0%) subjects withdrew consent in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively. Additionally, 5/100 (5.0%) subjects withdrew due to lack of efficacy in the aripiprazole 10-mg arm as determined by the investigator, compared with 1/102 (1.0%) in the aripiprazole 30-mg arm and 1/100 (1.0%) in the placebo arm.

The three treatment arms were demographically similar and had similar baseline disease characteristics. The majority of subjects were male (171/302, 56.6%), Caucasian (180/302, 60.0%), and non−Hispanic (261/302, 86.0%). The mean age was 15.5 years (range, 13.0 to 17.0 years).

Overall, the baseline disease severity was comparable across all treatment arms. The mean PANSS Total Score and Children's Depression Rating Scale - Revised (CDRS-R) Suicidal Ideations Score was 94.1 and 1.3, respectively. A total of 223/302 (74.0%) subjects had received treatment for previous episodes.

**Efficacy Results:**

Primary Efficacy Variable:

The PANSS Total Scores at baseline were similar across treatment arms, with mean scores of 93.7, 94.9, and 95.0 in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms, respectively. Aripiprazole 10 mg and 30 mg showed statistically significant improvements over placebo at Week 6. Using the LOCF data set, the PANSS Total Score changes from baseline to Week 6 were −26.7 in the aripiprazole 10-mg arm, −28.6 in the aripiprazole 30-mg arm, and −21.2 in the placebo arm. The comparison between aripiprazole and placebo was significant at both doses (p=0.0414 for aripiprazole 10 mg and p=0.0061 for aripiprazole 30 mg). Similar results were observed in the analysis using the OC data set, with changes from baseline to Week 6 of −30.6 in the aripiprazole 10-mg arm, −31.9 in the aripiprazole 30-mg arm, and −22.3 in the placebo arm. The comparison between aripiprazole and placebo was significant at both doses (p=0.0011 for aripiprazole 10 mg and p=0.0002 for aripiprazole 30 mg). The mean changes from baseline in PANSS Total Score by week are presented in the following table using LOCF:

| Mean Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score by Week (LOCF) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit/Week** | **Aripiprazole 10 mg** | | **Aripiprazole 30 mg** | | **Placebo** | | **P-value[b] Aripiprazole 10 mg vs placebo** | **P-value[b] Aripiprazole 30 mg vs placebo** |
| | **N** | **LS Me[a]** | **N** | **LS Me[a]** | **N** | **LS Me[a]** | | |
| Baseline[c] | 99 | 93.7 | 97 | 94.9 | 98 | 95.0 | 0.5375 | 0.9372 |
| Week 1 | 98 | -6.9 | 95 | -10.4 | 97 | -7.2 | 0.8390 | 0.0465 |
| Week 2 | 99 | -13.9 | 97 | -15.2 | 98 | -12.5 | 0.4748 | 0.1828 |
| Week 3 | 99 | -18.4 | 97 | -22.1 | 98 | -16.7 | 0.4759 | 0.0269 |
| Week 4 | 99 | -21.8 | 97 | -24.6 | 98 | -19.0 | 0.2346 | 0.0181 |
| Week 5 | 99 | -24.5 | 97 | -27.3 | 98 | -20.3 | 0.0979 | 0.0057 |
| Week 6[d] | 99 | -26.7 | 97 | -28.6 | 98 | -21.2 | 0.0414 | 0.0061 |

vs = versus.

[a] The LS means were the adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata. 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 Variables:

*PANSS Total Score at All Visits Other Than Week 6:* Using the LOCF data set, the aripiprazole 10-mg arm showed improvements over the placebo arm in the change from baseline in PANSS Total Score at all visits; however, the improvements were statistically significant compared with placebo only at Week 6 (see above). Using the OC data set, the aripiprazole 10-mg arm showed statistically significant improvements over the placebo arm in the change from baseline in PANSS Total Score at Weeks 4 through 6 as follows: Week 4 (−24.0 versus −19.3, p=0.0347), Week 5 (−27.6 versus −21.7, p=0.0124), and Week 6 (−30.6 versus −22.3, p=0.0011). The aripiprazole 30-mg arm showed statistically significant improvements over placebo in the change from baseline in PANSS Total Score at Week 1, Week 3, Week 4, Week 5, and Week 6 (LOCF). Using the OC data set, the aripiprazole 30-mg arm showed statistically significant improvements over placebo at Weeks 3 through 6 as follows: Week 3 (−23.4 versus −17.9, p=0.0200), Week 4 (−26.4 versus −19.3, p=0.0016), Week 5 (−30.4 versus −21.7, p=0.0003), and Week 6 (−31.9 versus -22.3, p=0.0002) (OC).

*CGAS Score:* For the change from baseline in CGAS Score, a positive LS mean indicated improvement. 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 Week 6 using the LOCF and OC data sets. At Week 6, the mean changes from baseline using LOCF were 14.7, 14.8, and 9.8 in the aripiprazole 10-mg, 30-mg, and placebo arms, respectively (p=0.0054 for 10 mg versus placebo and p=0.0044 for 30 mg versus placebo). Similar results were observed using the OC data set.

*CGI-Severity Score:* For the change from baseline in CGI-Severity Score, a negative LS mean indicated improvement. For the mean change from baseline in CGI-Severity Score using the LOCF data set, the aripiprazole 10-mg arm showed statistically significant improvements over the placebo arm at Week 3 (−0.8 versus −0.6, p=0.0399), Week 5 (−1.1 versus −0.8, p=0.0252), and Week 6 (−1.2 versus −0.9, p=0.0071). Using the OC data set, the aripiprazole 10-mg arm showed statistically significant improvements over placebo at Week 3, (−0.8 versus −0.6, p=0.0252), Week 4 (−1.0 versus −0.7, p=0.0109), Week 5 (−1.2 versus −0.8, p=0.0016), and Week 6 (−1.4 versus −0.9, p=0.0001). The aripiprazole 30-mg arm showed statistically significant improvements over placebo in the mean change from baseline in CGI-Severity Score using the LOCF data set at Week 1 (−0.3 versus −0.2, p=0.0210), Week 3 (−0.9 versus −0.6, p=0.0023), Week 4 (−1.0 versus −0.8, p=0.0158), Week 5 (−1.1 versus −0.8, p=0.0031), and Week 6 (−1.3 versus −0.9, p=0.0016). Statistically significant improvements over placebo in the aripiprazole 30-mg arm were observed using the OC data set at Week 1 (−0.3 versus −0.2, p=0.0210), Week 3 (−0.9 versus −0.6, p=0.0045), Week 4 (−1.1 versus −0.7, p=0.0083), Week 5 (−1.2 versus −0.8, p=0.0009), and Week 6 (−1.4 versus −0.9, p=0.0003).

*CGI-Improvement Score:* For the CGI-Improvement, a lesser mean score indicated improvement. Using the LOCF data set, the aripiprazole 10-mg arm showed statistically significant improvements over the placebo arm at Week 1 (3.6 versus 3.8, p=0.0175), Week 5 (2.8 versus 3.2, p=0.0239), and Week 6 (2.7 versus 3.1, p=0.0167). Using the OC data set, the aripiprazole 10-mg arm showed statistically significant improvements over placebo in the CGI-Improvement Score at Week 1 (3.6 versus 3.8, p=0.0175), Week 3, (2.9 versus 3.2, p=0.0220), Week 4 (2.7 versus 3.1, p=0.0029), Week 5 (2.6 versus 3.1, p=0.0009), and Week 6 (2.3 versus 3.0, p=0.0001). The aripiprazole 30-mg arm showed statistically significant improvements over placebo using the LOCF data set at Week 1 (3.4 versus 3.8, p=0.0013), Week 3 (2.8 versus 3.2, p=0.0044), Week 4 (2.7 versus 3.2, p=0.0033), Week 5 (2.6 versus 3.2, p=0.0002), and Week 6 (2.5 versus 3.1, p=0.0004). Statistically significant improvements over placebo in the aripiprazole 30-mg arm were also observed using the OC data set at Week 1 (3.4 versus 3.8, p=0.0013), Week 3 (2.8 versus 3.2, p=0.0031), Week 4 (2.6 versus 3.1, p=0.0004), Week 5 (2.4 versus 3.1, p<0.0001), and Week 6 (2.3 versus 3.0, p<0.0001).

*PANSS Positive Subscale Score:* For the change from baseline in PANSS Positive Subscale Score, a negative LS mean indicated improvement. Improvements over placebo in the mean change from baseline in PANSS Positive Subscale Scores were observed for both the aripiprazole 10-mg and 30-mg arms at all time points using the LOCF and OC data sets. The aripiprazole 10-mg arm showed statistically significant improvements over the placebo arm at Week 5 (−7.2 versus −5.6, p=0.0276) and Week 6 (−7.6 versus −5.6, p=0.0134) using the LOCF data set, and at Week 4 (−7.2 versus −5.4, p=0.0066), Week 5 (−8.2 versus −5.9, p=0.0010), and Week 6 (−8.8 versus −5.9, p<0.0001) using the OC data set. The aripiprazole 30-mg arm showed statistically significant improvements over placebo at Week 1 (−2.9 versus −1.8, p=0.0256), Week 3 (−6.2 versus −4.6, p=0.0270), Week 4 (−7.1 versus −5.3, p=0.0118), Week 5 (−7.8 versus −5.6, p=0.0029), and Week 6

(−8.1 versus −5.6, p=0.0018) (LOCF). Similar results were observed for the aripiprazole 30-mg arm using the OC data set.

*PANSS Negative Subscale Score*: For the change from baseline in PANSS Negative Subscale Score, a negative LS mean indicated improvement. The aripiprazole 10-mg arm showed statistically significant improvements over the placebo arm in the mean change from baseline in PANSS Negative Subscale Score at Week 6 (−6.9 versus −5.4, p=0.0462) (LOCF). Similar results were observed for the aripiprazole 10-mg arm using the OC data set. The aripiprazole 30-mg arm showed statistically significant improvements over placebo at Week 3 (−5.4 versus −4.0, p=0.0410) and Week 4 (−6.0 versus −4.6, p=0.0427) using the LOCF data set. Using the OC data set, the aripiprazole 30-mg arm showed statistically significant improvements over placebo at Week 3 (−5.6 versus −4.2, p=0.0343), Week 4 (−6.4 versus −4.6, p=0.0075), Week 5 (−7.1 versus −5.2, p=0.0106), and Week 6 (−7.5 versus −5.4, p=0.0068).

*Time to Discontinuation Due to All Reasons:* 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.

Other Efficacy Analyses:
*PANSS Total Score Responders (at least a 30% decrease from baseline):* The percentage of subjects responding to treatment with a ≥30% decrease from baseline in PANSS Total Score was statistically significantly greater in the placebo arm than the aripiprazole 10-mg arm at Week 1 using both the LOCF and OC data sets (1.0% versus 6.2%, p=0.0475). The percentage of subjects responding to treatment with a ≥30% decrease from baseline in PANSS Total Score was statistically significantly greater than placebo for the aripiprazole 10-mg arm at Week 4 using both the LOCF (35.4% versus 21.4%, p=0.0305) and OC (37.9% versus 22.0%, p=0.0230) data sets, and for the aripiprazole 30-mg arm at Week 3, Week 4, and Week 5 using both the LOCF (33.0% versus 17.4%, p=0.0108; 43.3% versus 21.4%, p=0.0010; and 43.3% versus 28.6%, p=0.0347, respectively) and OC (34.4% versus 18.3%, p=0.0118; 44.7% versus 22.0%, p=0.0006; and 48.8% versus 30.7%, p=0.0256, respectively) data sets.

**Pharmacokinetic Results:** The concentration data and calculated time postdose were reviewed for correctness; errors and discrepancies were noted and, if possible, corrections were noted. The results of the population PK analyses will be reported separately.

**Safety Results:** A total of 202 subjects were exposed to aripiprazole: 100 in the 10-mg arm at average doses ranging from 6.2 mg to 10.0 mg, and 102 in the 30-mg arm at average doses ranging from 6.9 mg to 30.0 mg. A total of 100 subjects were exposed to placebo. The percentage of subjects exposed to trial drug for 36 to 42 days was 86/100 (86.0%) in the aripiprazole 10-mg arm at an average dose of 9.5 mg; 84/102 (82.4%) in the aripiprazole 30-mg arm at an average dose of 27.8 mg; and 90/100 (90.0%) in the placebo arm.

A total of 188 treatment-emergent adverse events (TEAEs) were experienced by 71/100 (71.0%) subjects in the aripiprazole 10-mg arm; 232 TEAEs were experienced by 74/102 (72.5%) subjects in the aripiprazole 30-mg arm; and 147 TEAEs were experienced by 57/100 (57.0%) subjects in the placebo arm. The most common TEAEs reported at an incidence rate of ≥5% in the aripiprazole 10-mg arm were headache (16.0%), extrapyramidal disorder (13.0%), somnolence (11.0%), insomnia (11.0%), nausea (9.0%), dizziness (7.0%), vomiting (5.0%), nasopharyngitis (5.0%), and akathisia (5.0%). In the aripiprazole 30-mg arm, the most common TEAEs reported at an incidence rate of ≥5% were extrapyramidal disorder (21.6%), somnolence (21.6%), tremor (11.8%), akathisia (11.8%), headache (10.8%), nausea (9.8%), and insomnia (9.8%). In the placebo arm, the most common TEAEs were insomnia (15.0%), headache (10.0%), somnolence (6.0%), nausea (6.0%), vomiting (5.0%), akathisia (5.0%), extrapyramidal disorder (5.0%), and agitation (5.0%). There appeared to be a general trend of increasing incidence across the treatment groups for the commonly reported TEAEs of nausea, akathisia, extrapyramidal disorder, somnolence, and tremor, with the highest incidence in the aripiprazole 30-mg arm.

The most common potentially drug-related TEAEs reported at an incidence rate of ≥5% in the aripiprazole 10-mg arm were extrapyramidal disorder (13.0%), somnolence (10.0%), headache (9.0%), dizziness (7.0%), insomnia (7.0%), nausea (6.0%), and akathisia (5.0%). In the aripiprazole 30-mg arm, the most common potentially drug related TEAEs were extrapyramidal disorder (21.6%), somnolence (20.6%), akathisia (11.8%), tremor (10.8%), and nausea (7.8%). In the placebo arm, the most common potentially drug-related TEAEs were insomnia (8.0%) and somnolence (5.0%). Of the commonly reported potentially drug-related TEAEs, there appeared to be a general trend of increasing incidence across the treatment groups for TEAEs of nausea, akathisia, extrapyramidal disorder, somnolence, and tremor, with the highest incidence in the aripiprazole 30-mg group.

No deaths were reported in this trial. The percentage of subjects who experienced SAEs was similar across the 3 treatment arms: 4/100 (4.0%) and 4/102 (3.9%) in the aripiprazole 10-mg and 30-mg arms, respectively, and 3/100 (3.0%) in the placebo arm. The most commonly reported SAEs overall were psychotic disorder (1 subject in each treatment arm) and schizophrenia (1 subject in each aripiprazole treatment arm). The following SAEs were reported by 1 subject each in the aripiprazole 10-mg arm: extrapyramidal disorder, possible neuroleptic malignant syndrome, aggression, psychotic disorder, schizophrenia, and thrombophlebitis. In the aripiprazole 30-mg arm, the following SAEs were reported by 1 subject each: varicella, depression, psychotic disorder, schizophrenia, and suicidal ideation. In the placebo arm, intentional overdose, overdose, psychotic disorder, and suicide attempt were each reported by 1 subject. An additional non-serious TEAE of suicidal ideation was experienced by one subject in the placebo group.

The percentage of subjects who discontinued trial medication due to TEAEs was greater in the aripiprazole 10-mg arm (7/100, 7.0%) than in the aripiprazole 30-mg arm (4/102,

3.9%) or the placebo arm (2/100, 2.0%). The most commonly reported TEAEs resulting in discontinuation of trial medication (reported by more than 1 subject overall) were psychotic disorder (1 subject in each treatment arm) and schizophrenia (2 subjects in the aripiprazole 10-mg arm and 1 subject in the aripiprazole 30-mg arm). Other TEAEs resulting in discontinuation of trial medication were: dystonia, somnolence, anxiety, and hypomania (1 subject each) in the aripiprazole 10-mg arm; nausea and varicella (1 subject each) in the aripiprazole 30-mg arm; and overdose (1 subject) in the placebo arm. Overall, 2 subjects in each treatment arm reported SAEs resulting in discontinuation of trial medication: psychotic disorder (1 subject in each treatment arm), schizophrenia (1 subject in the aripiprazole 10-mg arm), varicella (1 subject in the aripiprazole 30-mg arm), and overdose (1 subject in the placebo arm).

No clinically relevant mean changes were observed in the results for the serum chemistry, hematology, or urinalysis laboratory tests, vital signs, or ECG parameters. Statistically significant decreases from baseline to Day 42 and last visit in mean QT and QTc (QTcB, QTcF, QTcN, and QTcE) intervals were observed in the 30 mg aripiprazole arm compared to placebo; however none were reported as TEAEs and the changes were not considered clinically meaningful. Overall, no clinically meaningful trends were observed for any of the potentially clinically significant laboratory test abnormalities. A low incidence of clinically significant hyperprolactinemia was observed in the trial: 3/98 (3.1%) in the aripiprazole 10-mg arm, 0/92 (0.0%) in the aripiprazole 30-mg arm, and 6/96 (6.3%) in the placebo arm. Although several abnormalities in laboratory tests, vital signs, and ECG parameters were reported as TEAEs, all appeared to be isolated findings. None of these TEAEs were reported as SAEs or resulted in discontinuation of trial medication.

No clinically relevant mean changes were observed in the insulin or fasting insulin results. Two types of abnormal insulin laboratory test results were reported as TEAEs: increased blood insulin (2 subjects in the aripiprazole 10-mg arm) and hyperinsulinaemia (1 subject in the aripiprazole 10-mg arm); neither of these TEAEs was reported as an SAE or resulted in discontinuation of trial medication.

A mean decrease in prolactin levels relative to baseline was observed overall across all treatment groups. The mean change from baseline to Day 42 in prolactin levels was −8.82 ng/mL, −11.94 ng/mL, and −16.74 ng/mL in the placebo, aripiprazole 10-mg, and aripiprazole 30-mg arms, respectively, when all subjects tested were included in the analysis. When analyzed by gender, similar results were observed for males. The mean change from baseline to Day 42 in prolactin levels for males was −4.21 ng/mL, −9.62 ng/mL, and −14.69 ng/mL in the placebo, aripiprazole 10-mg, and aripiprazole 30-mg arms, respectively. For females, the decreases in prolactin levels were greater than for males in both aripiprazole arms; however, they were also greater in the placebo arm. The mean change from baseline to Day 42 in prolactin levels for females was −15.81 ng/mL, −13.70 ng/mL, and −20.62 ng/mL in the placebo, aripiprazole 10-mg, and aripiprazole 30-mg arms, respectively.

The overall 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 was greatest in the aripiprazole 10-mg arm (33/98, 33.7%), followed by the aripiprazole 30-mg arm (25/95, 26.3%), and then by the placebo arm (8/96, 8.3%). For males, the incidence of low prolactin levels was 17/44 (38.6%) in the aripiprazole 10-mg arm, 19/60 (31.7%) in the aripiprazole 30-mg arm, and 4/57 (7.0%) in the placebo arm. For females, the incidence of low prolactin levels was 16/54 (29.6%) in the aripiprazole 10-mg arm, 6/35 (17.1%) in the aripiprazole 30-mg arm, and 4/39 (10.3%) in the placebo arm. None of these events were reported as TEAEs or SAEs or resulted in discontinuation of trial medication.

The EPS-related side effects (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. Several TEAEs associated with EPS related symptoms were reported more frequently with aripiprazole treatment than with placebo, the most common of which (≥5% incidence in any treatment arm) were akathisia (5/100 [5.0%] in the aripiprazole 10-mg arm, 12/102 [11.8%] in the aripiprazole 30-mg arm, and 5/100 [5.0%] in the placebo arm); extrapyramidal disorder (13/100 [13.0%] in the aripiprazole 10-mg arm, 22/102 [21.6%] in the aripiprazole 30-mg arm, and 5/100 [5.0%] in the placebo arm); and tremor (2/100 [2.0%] in the aripiprazole 10-mg arm, 12/102 [11.8%] in the aripiprazole 30-mg arm, and 2/100 [2.0%] in the placebo arm). The incidence of these TEAEs, as well as that for the following EPS-related TEAEs increased with dose of aripiprazole: salivary hypersecretion, gait disturbance, drooling, dyskinesia, and myoclonus. The majority of these events were mild or moderate in severity and only one (event of dystonia on the 30-mg arm) resulted in discontinuation of the trial medication.

The metabolic syndrome evaluation included assessment of the following tests: fasting blood levels for triglycerides, HDL-C, and glucose; waist circumference; BMI; and supine and standing systolic and diastolic BP. 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 evaluation parameters. Notably, for all subjects, the incidences of abnormalities for both waist circumference and BMI were comparable or decreased at the last visit compared with baseline for all 3 treatment arms. At the last visit, the percentage of subjects who experienced a potentially clinically significant weight gain (≥7% weight gain compared to baseline) was 4/99 (4.0%) in the aripiprazole 10-mg arm, 5/97 (5.2%) in the aripiprazole 30-mg arm, and 1/98 (1.0%) in the placebo arm. The percentage of subjects who experienced a potentially clinically significant weight loss (≥7% weight loss compared to baseline) at the last visit was 3/99 (3.0%) in the aripiprazole 10-mg arm, 2/97 (2.1%) in the aripiprazole 30-mg arm, and 6/98 (6.1%) in the placebo arm. Overall, the mean weight and BMI z-scores for each visit were within 0.5 standard deviations (SD) of the general population for all 3 treatment arms, and the changes from baseline were negligible. At the last visit, the mean (SD) change from baseline in weight z-score was 0.00 (0.28) with a range of −1.31 to

1.54 in the aripiprazole 10-mg arm; 0.00 (0.20) with a range of −0.76 to 0.46 in the aripiprazole 30-mg arm; and −0.11 (0.22) with a range of −0.98 to 0.39 in the placebo arm. At the last visit, the mean (SD) change from baseline in BMI z-score was 0.01(0.26) with a range of −1.08 to 1.07 in the aripiprazole 10-mg arm; 0.01 (0.25) with a range of −1.07 to 0.80 in the aripiprazole 30-mg arm; and −0.12 (0.27) with a range of −0.99 to 0.56 in the placebo arm. Similar results were observed for the mean change from baseline in BMI z-scores for males and for females.

Based on a comparison of the results of five short-term adult studies in schizophrenia (ie, Studies 31-97-201, N=414; 31-97-202, N=404; CN138001, N=420, 31-93-202, N=103; 31-94-202, N=307; total N=1648) with the results of this pediatric schizophrenia trial, the safety profile of aripiprazole in adolescents with the diagnosis of schizophrenia is comparable to the adult schizophrenia population, with the exception of dose-related occurrence of higher frequency of somnolence and extrapyramidal symptoms observed in the pediatric population.

**Other Outcome Measures:**

*P-QLES-Q Total Score:* Using the LOCF data set, improvements were observed in the mean change from baseline to Week 6 in the P-QLES-Q Total Score in all 3 treatment arms; however, no statistically significant differences were observed between either of the aripiprazole arms and placebo. Similar results were seen with the analysis of the OC data set.

*P-QLES-Q Overall Score:* Using the LOCF data set, baseline scores were statistically significantly higher in the placebo arm than in the aripiprazole 10-mg arm (p=0.0477). At Week 6, statistically significant improvements compared to placebo were seen in the aripiprazole 10-mg arm (0.6 versus 0.1, p=0.0045) and the aripiprazole 30-mg arm (0.6 versus 0.1, p=0.0030). Similar results were observed using the OC data set.

*Hospitalizations Due to Worsening of Schizophrenia:* Overall, 75/302 (24.8%) subjects were hospitalized during the trial. Per regulatory request in Argentina, subjects were required to be hospitalized for the first 2 weeks of the trial, with extended hospitalization as needed. The incidence of hospitalization was similar across treatment arms: 23/100 (23.0%) in the aripiprazole 10-mg arm, 27/102 (26.5%) in the aripiprazole 30-mg arm, and 25/100 (25.0%) in the placebo arm. Of those hospitalized, the incidence of subjects hospitalized due to worsening of schizophrenia was low. When Argentina was excluded from the analysis, a total of 60/287 (20.9%) of subjects were hospitalized during the trial: 19/96 (19.8%) in the aripiprazole 10-mg arm, 21/96 (21.9%) in the aripiprazole 30-mg arm, and 20/95 (21.1%) in the placebo arm. The incidences of hospitalizations due to worsening of schizophrenia were similar in the analysis with or without sites from Argentina.

Among subjects who were inpatients at the start and end of the trial, 1/100 (1.0%) subject in the aripiprazole 10-mg arm was hospitalized due to worsening of schizophrenia. Among subjects who were outpatients at the start of the trial and inpatients at the end of

the trial, 4 subjects were hospitalized due to worsening of schizophrenia: 2/100 (2.0%) in the aripiprazole 10-mg arm, 1/102 (1.0%) in the aripiprazole 30-mg arm, and 1/100 (1.0%) in the placebo arm. No other subjects were hospitalized due to worsening of schizophrenia.

**Conclusions:**

- Aripiprazole was effective in the treatment of adolescent subjects with schizophrenia at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared with placebo in the primary efficacy endpoint, PANSS Total Score at Week 6 (LOCF). For the aripiprazole 30-mg arm, the onset of statistically significant improvement over placebo was at Week 1, then Week 3 and continuing to Week 6. For the aripiprazole 10-mg arm, statistically significant improvement over placebo was observed at Week 6.

- Aripiprazole 10 mg and 30 mg were effective at Week 6 in the treatment of schizophrenia in adolescents based on statistically significant improvements compared with placebo in secondary efficacy endpoints (LOCF) that included change from baseline in PANSS Positive Subscale Score, CGAS Score, and CGI-Severity Score, and in addition mean CGI-Improvement Score. Aripiprazole 10 mg was also effective at Week 6 based on statistically significant improvements compared with placebo in the secondary efficacy endpoint (LOCF) of change from baseline in PANSS Negative Subscale Score.

- Overall subject retention was high in this trial, with approximately 84%, 82%, and 90% completion rates in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms, respectively. No statistically significant differences were observed between the treatment arms with respect to time to discontinuation due to all reasons.

- Aripiprazole was generally safe and well tolerated at daily doses of 10 mg and 30 mg in adolescents with schizophrenia in this trial, with the majority of TEAEs reported as mild or moderate. However, the 10-mg dose was better tolerated than the 30-mg dose based on a lower number of TEAEs and lower incidence of EPS events in the 10-mg dose. There appeared to be a general trend of increasing incidence across the treatment groups for TEAEs of nausea, akathisia, extrapyramidal disorder, somnolence, and tremor, with the highest incidence in the aripiprazole 30-mg arm.

- There was 1 suicidal ideation event in the aripiprazole 30-mg arm (1%) and 1 suicidal attempt and 1 suicidal ideation (1% each) in the placebo arm.

- An overall low incidence of clinically significant hyperprolactinemia was observed in this trial: 3% in the aripiprazole 10-mg arm, 0% in the aripiprazole 30-mg arm, and 6% in the placebo arm. While there appeared to be a mean decrease in prolactin levels relative to baseline across all treatment groups, no

clinically meaningful conclusion can be derived from the observed data. The incidences of low prolactin levels were 8%, 34%, and 26%, respectively, in the placebo, aripiprazole 10 mg, and aripiprazole 30-mg arms.

- Statistically significant decreases in mean QT and QTc intervals were observed compared to placebo; however none were considered to be clinically meaningful.

- There was no signal of increased abdominal obesity associated with aripiprazole in this trial. No clinically meaningful changes were observed in weight z-scores or BMI z-scores or in the overall evaluation of metabolic syndrome.

- Based on a comparison of the results of five short-term adult studies in schizophrenia with the results of this pediatric schizophrenia trial, the safety profile of aripiprazole in adolescents with the diagnosis of schizophrenia is comparable to the adult schizophrenia population, with the exception of dose-related occurrence of higher frequency of somnolence and extrapyramidal symptoms observed in the pediatric population.

- Aripiprazole 10 mg and 30 mg demonstrated a quality of life benefit in adolescent subjects with schizophrenia based on statistically significant improvements compared with placebo in the P-QLES-Q Overall Score at Week 6 (LOCF).

- The efficacy of aripiprazole has been established in the treatment of adolescent subjects with schizophrenia at daily doses of 10 mg and 30 mg. The recommended target dose of aripiprazole in adolescents with schizophrenia is 10 mg QD. The starting dose in these patients was 2 mg, which was titrated to 5 mg after 2 days and to the target dose of 10 mg after 2 additional days. A daily dose of 30 mg can be more effective for some individual patients but tolerability should be monitored carefully in order to properly assess the risk/benefit ratio.

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[1] Volkmar F. Childhood and adolescent psychosis: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry. 1996 Jul;35(7):843-51.

[2] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC. American Psychiatric Association. 1994.

[3] American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry. 2001;40(7, Suppl):4S-23S.

[4] Remschmidt J, Schulz E, Herpertz-Dahlmann B. Schizophrenic psychoses in childhood and adolescence. CNS Drugs. 1996;6(2):100-12.

[5] American Psychiatric Association. Practice guidelines for the treatment of patients with schizophrenia. Am J Psychiatry. 1997;154(4 Suppl):1-63.

[6] Kornhauser D. Tolerability, pharmacokinetics, and pharmacodynamics of aripiprazole during oral administration in children and adolescents with conduct disorder. Bristol-Myers Squibb Study/Report No. CN138014, 2006.