Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597)

Clinical Summary for Protocol 31-05-243
NCT No. 01001702

An Open-Label Rollover Study for Subjects with Schizophrenia Completing ABILIFY® (Aripiprazole) Clinical Study 31-03-241

Indication: Schizophrenia

Clinical Development Phase: 3B

Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.
Rockville, Maryland, United States

Trial Initiation Date: 06 Apr 2006

Trial Completion Date: 23 Jul 2012

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: An Open-Label Rollover Study for Subjects with Schizophrenia Completing ABILIFY® (Aripiprazole) Clinical Study 31-03-241

Trial Center(s) by Region: Multicenter (35 centers; Multinational)

Clinical Phase/Trial Type: Phase 3B/Open-label, multicenter, non-comparative therapeutic use trial

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: Abilify® (aripiprazole, Bristol-Myers Squibb [BMS]-337039, Otsuka Pharmaceutical Company, Ltd [OPC]-14597) is a novel dopamine-serotonin system stabilizer discovered by OPC and co-developed by BMS and OPC. Abilify® (hereafter, referred to as aripiprazole) oral tablets are approved in the United States (US) for the treatment of adults with acute schizophrenia, maintenance of stability in adults with schizophrenia, treatment of acute manic episodes associated with bipolar I disorder in adults and pediatric patients, maintenance of efficacy in adults with bipolar I disorder, and as adjunctive treatment of major depressive disorder (MDD). Aripiprazole is also approved for the treatment of schizophrenia in the European Union (EU), Australia, and a number of countries in Asia, Europe, and Latin America. In addition, an intramuscular (IM) injection formulation, an oral solution formulation, and an orally disintegrating (dispersible) tablet formulation of aripiprazole have been approved in the US and EU. The aripiprazole injection formulation is approved for the treatment of agitation associated with schizophrenia or bipolar disorder, manic or mixed episodes in the US and EU. Additional clinical trials of the IM depot formulation for maintenance treatment of schizophrenia are ongoing and planned.

In pediatrics, aripiprazole is indicated for the treatment of schizophrenia in the US (ages 13 to 17 years) and EU (ages 15 to 17 years), for the treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy or adjunctive therapy to either lithium or valproate in the US (ages 10 to 17 years), and for the treatment of irritability associated with autistic disorder in children and adolescents in the US (ages 6 to 17 years).

Publications: None to date.

Objectives: The primary objective of this trial was to continue to provide aripiprazole therapy (5 mg, 10 mg, and/or 15 mg tablets) to subjects with schizophrenia who completed the Otsuka-sponsored open-label safety and tolerability Trial 31-03-241.

Methodology: Trial 31-05-243 was an open-label, multicenter, non-comparative rollover trial designed to continue to provide aripiprazole on a compassionate use basis in doses ranging from 5 to 30 mg to adolescent (13 to 17 years of age) and adult

(adolescents who reach 18 years during the open-label parent trial [Trial 31-03-241] or previous double-blind trial [Trial 31-03-239]) male and female subjects with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV). Subjects were required to complete Trial 31-03-241 in order to be eligible for the current rollover trial. Trial 31-03-241 was a multicenter, open-label trial that provided up to 6 months of aripiprazole for subjects completing Trial 31-03-239, a randomized, comparative trial in which adolescents with a DSM-IV diagnosis of schizophrenia received double-blind treatment (aripiprazole or placebo) for 6 weeks. The DSM-IV diagnosis of schizophrenia was as confirmed by a Kiddie-Sads-Present and Lifetime Version interview initially conducted for eligibility to enroll in Trial 31-03-239 (no additional confirmatory diagnostic evaluations were performed for Trial 31-03-241 or the current trial).

This trial was intended for countries where aripiprazole was not yet commercially available and/or reimbursed. This trial was conducted in Argentina, Bulgaria, Croatia, India, Russian Federation, Serbia and Montenegro, South Africa, and Ukraine at 35 trial centers (one additional center was initiated but did not enroll subjects).

Informed consent from the responsible adult (or potentially from the subject if 18 years of age) and assent of the child (if applicable) were obtained and documented with the opportunity to have all questions answered prior to completion of any trial-related assessments. Participation in the rollover trial was considered on an individual basis if enrollment criteria were met. Subjects retained the same identification number throughout the open-label and double-blind trials.

The End of Treatment (EOT) evaluations conducted at the last visit of Trial 31-03-241 served as the baseline evaluations for Trial 31-05-243. Subjects attended 4 trial visits during the first year of treatment (Months 3, 6, 9, and 12), 3 visits during the second year of treatment (Months 15, 18, and 24), and visits every 6 months thereafter (Months 30, 36, 42, 48, 54, 60, 66, and 72/early termination [ET]). Subjects were contacted by phone at monthly intervals between scheduled visits to assess the occurrence of adverse events (AEs). Follow-up phone calls were made 14 (± 2) days after the last trial visit to assess the status of ongoing AEs and to record the occurrence of new serious AEs (SAEs). Each subject received daily aripiprazole at a dose between 5 and 30 mg (maximum allowed dose), as previously established in the 31-03-241 safety and tolerability trial; however, modifications to the daily dose could be made at the investigator's discretion, if clinically warranted.

Subjects who enrolled into this trial were permitted to receive psychotropic medications with the exception of other antipsychotic agents and could continue any concomitant medications permitted during Trial 31-03-241. Safety data were derived from AE reporting, physical examinations, clinical laboratory tests, urine pregnancy tests (all female subjects), electrocardiograms (ECG), and measurements of vital signs (including body weight), body mass index (BMI), and waist circumference. A Clinical Global Impression - Severity (CGI-S) scale was completed to assess the continuation of

therapeutic benefit from aripiprazole treatment as determined by the investigator. The Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) was completed to assess the subject's perception of treatment benefit and was administered in translated languages, when available. The Columbia-Suicide Severity Rating Scale (C-SSRS) was administered to assess the risk of suicide events and to classify reported suicide events (per Amendment 003 of trial protocol, approved 28 Oct 2009).

Aripiprazole treatment and trial visits continued until there was a clinical or administrative reason for discontinuation. Clinical reasons included, but were not limited to: voluntary withdrawal, treatment intolerance, lost to follow-up, and lack of continued benefit per the investigator. Administrative reasons included, but were not limited to: commercial availability of and/or reimbursement for aripiprazole, termination of aripiprazole development by the sponsor, or the trial reached the planned trial end date of 31 Dec 2012. Once aripiprazole became commercially available and/or reimbursed in the country where a subject was participating in the trial, treatment with aripiprazole in Trial 31-05-243 was to be discontinued within a reasonable period of time (approximately 1 to 3 months) and the subject was to be transitioned to commercially available aripiprazole (Abilify®) or another treatment option as deemed appropriate by the investigator.

For purposes of this trial, subjects who completed the last scheduled visit during the treatment period, ie, the Month 72 visit (or the last scheduled visit within 6 months before 31 Dec 2012), were defined as trial completers.

Number of Subjects: Subjects were directly enrolled into the current open-label, non-comparative rollover trial from the previous open-label parent Trial 31-03-241; therefore, no predetermined sample size was calculated. A maximum of 200 subjects were expected to be enrolled. A total of 85 subjects who completed Trial 31-03-241 were actually enrolled. All 85 enrolled subjects were included in the safety analysis. A total of 84/85 subjects (98.8%) were included in the analysis of efficacy and quality of life outcome measures.

Diagnosis and Main Criteria for Inclusion/Exclusion: This trial enrolled male and female adolescent (13 to 17 years of age) and adult (adolescents who reached 18 years during participation in the previous double-blind efficacy trial [Trial 31-03-239] or the open label parent trial [Trial 31-03-241]) subjects with a confirmed diagnosis of Axis I schizophrenia (DSM-IV) who had completed the Otsuka-sponsored open-label safety and tolerability Trial 31-03-241. Subjects who had a significant risk of committing suicide based on history, those with newly diagnosed diabetes, those who had epilepsy, a history of seizure, head trauma, stroke, or any other unstable medical condition, or a co-morbid serious, uncontrolled systemic illness were excluded, as were those who were sexually active and who did not agree to use the approved methods of contraception, and women who were pregnant.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Aripiprazole was manufactured by either Otsuka Pharmaceutical Co., Ltd. (Japan) or Bristol-Myers Squibb Co. (Mayaguez, Puerto Rico) and provided through commercial supply as oral tablets in strengths of 5 mg, 10 mg, and 15 mg for use as flexible doses ranging from 5 to 30 mg/day . All trial medication was provided in bottles containing 30 tablets in each bottle and dispensed as a 3-month supply.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Not Applicable

Duration of Treatment: Once eligibility was confirmed, subjects were eligible to receive aripiprazole treatment until aripiprazole became commercially available and/or reimbursed, the commercial availability of aripiprazole was terminated by the sponsor, or up until the trial end date of 31 Dec 2012, whichever occurred sooner. The Month 72 visit (or the last scheduled visit within 6 months before 31 Dec 2012) was to serve as the final trial completion visit, as well as the early termination (ET) visit.

Trial Assessments:
Efficacy: CGI-S, P-QLES-Q Total and Overall score

Safety: AEs, clinical laboratory tests (serum chemistry, hematology, and urinalysis), physical examination, vital signs, ECGs, C-SSRS, and metabolic syndrome evaluation. For the purpose of this trial, fasting serum triglycerides, HDL-C, and glucose levels; BMI and waist circumference; and supine and standing systolic and diastolic blood pressure were also evaluated as part of the metabolic syndrome evaluation. Adverse events of special interest were also summarized.

Criteria for Evaluation:
Primary Outcome Measures: The following primary safety variables were summarized:

- Frequency and severity of treatment-emergent adverse events (TEAEs),
- Frequency and severity of treatment-emergent SAEs (including AEs related to clinical laboratory abnormalities), and
- Rates of discontinuation from the trial due to TEAEs.

Secondary Outcome Measures:
Safety variables:

- Reported AEs (in addition to the primary safety variables) including summarization of TEAEs by causality, severity, and gender, as well as the incidence of deaths;
- Clinical laboratory tests (including routine serum chemistry, hematology, and urinalysis analyses as well as creatine phosphokinase [CPK]; fasting insulin, serum glucose, triglycerides, high-density lipoprotein cholesterol [HDL-C]; glycosylated hemoglobin [HbA1c]; and serum prolactin);

- Vital sign parameters (supine and standing blood pressure and pulse rate, body temperature, and respiration rate) and physical examination (including height and weight for calculation of BMI and measurement of waist circumference);
- ECGs;
- Percentage of subjects showing significant weight gain or loss (weight gain or loss ≥ 7% relative to baseline);
- C-SSRS.

For the purpose of this report, fasting serum triglycerides, HDL-C, and glucose levels; BMI and waist circumference; and supine and standing systolic and diastolic blood pressure were also evaluated as part of the metabolic syndrome evaluation. Adverse events of special interest were also summarized.

Statistical Methods:
Efficacy Methods: Efficacy (CGI-S score) and other outcome variables (P-QLES-Q Total and Overall scores) were summarized as change from baseline using descriptive statistics. Subjects with missing baseline or post-baseline efficacy and other outcome 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 analyses by visit; an observed case (OC) analysis was considered more appropriate than data imputation. However, data were summarized for the last available visit as an additional evaluation of these variables. No inferential statistical analyses were performed for any efficacy, safety, or other outcome variables.

Safety Methods: Safety analyses were conducted on the safety dataset, defined as all enrolled subjects who received at least one dose of open-label trial medication. Safety data were summarized using descriptive statistics, as appropriate. Treatment-emergent adverse events for this analysis were defined as any AE with onset after the first dose of open-label aripiprazole in Trial 31-05-243 or any event which continued from baseline and became serious, was classified as related to trial drug, or resulted in death, discontinuation, interruption or reduction of dose. The incidences of TEAEs were summarized for all TEAEs, TEAEs by severity, potentially drug-related TEAEs, treatment-emergent SAEs, and discontinuations due to TEAEs. Adverse events were examined by gender as well as overall incidence.

Descriptive statistics were used to summarize original values, change from baseline at each scheduled visit, and change from baseline to the last visit for the continuous safety variables. Incidences of metabolic syndrome abnormalities were summarized by visit, overall and by gender. Potentially clinically significant changes in laboratory parameters, ECG findings, vital signs, weight, and metabolic syndrome abnormalities were identified using prospectively-defined criteria. The age of subjects on the date of the trial visit was used for age-dependent criteria. QT intervals were corrected for heart rate (QTc) based on several formulas, including Bazett's formula (QTcB). Data collected on the C-SSRS were listed for ongoing subjects as Amendment 003 to the protocol was implemented.

Summary of Results:

Baseline Data, Disposition, and Demographics: All 85 enrolled subjects received at least one dose of trial medication and were included in the safety analysis. A total of 84/85 subjects (98.8%) were analyzed for secondary efficacy and quality of life outcome measures. The majority of subjects remained in the trial for at least 24 months: 78.8% completed at least 12 months and 51.8% completed at least 24 months of treatment. Fourteen (of 85) enrolled subjects (16.5%) completed at least 66 months (5.5 years) of treatment with open-label aripiprazole in the trial; of these, 13 (of 85) subjects (15.3%) completed the trial.

Overall, 72/85 subjects (84.7%) were prematurely discontinued from the trial. The two most common reasons for discontinuation were the subject having met the withdrawal criteria (22/85 subjects, 25.9%) and the subject withdrew consent (19/85 subjects, 22.4%). The incidence of subjects who discontinued from the trial due to lack of efficacy was low (3/85 subjects, 3.5%). Seven (of 85) subjects (8.2%) discontinued from the trial due to AEs.

The number of male and female subjects enrolled in the trial was balanced (43 males, 42 females). The mean age at trial entry (defined as the last scheduled visit in the previous Trial 31-03-241) was 16.3 years (range 13 to 18 years). The majority of subjects (66/85, 77.7%) were between 13 to 17 years of age; the remaining subjects (19/85, 22.4%) were 18 years of age at trial entry. Mean BMI was relatively similar between males and female subjects (21.9 and 23.2 kg/m2, respectively). The majority of subjects were Caucasian (49/85, 57.7%); the remaining subjects were Asian (24/85, 28.2%), 'Other' (11/85, 12.9%), or American Indian or Alaska Native (1/85, 1.2%).

Efficacy Results: No primary efficacy variable was defined for this trial.

Secondary Efficacy: Severity of illness was rated at all scheduled trial visits. For CGI-S, a lesser mean score indicates less severity of illness. Evaluation of efficacy based on mean change from baseline in CGI-S score indicated that efficacy was generally maintained in subjects who had previously received flexible daily doses of open-label aripiprazole (5 to 30 mg) in Trial 31-03-241 and continued treatment with open-label aripiprazole in the current long-term safety and tolerability trial. Mean scores for CGI-S generally decreased from baseline at each successive post-baseline visit up to the Month 72 scheduled visit (mean change from baseline ranged from −0.15 at Month 3 [n = 81] to a maximum change of −0.64 at Month 66 [n = 14]). Overall, the mean change (SD) from baseline (mean = 2.37) to the last visit (mean = 2.11) for CGI-S was −0.26 (1.07) (n = 84).

Other Quality of Life Outcomes: The P-QLES-Q was completed by the subject twice a year in translated languages to assess the subject's quality of life (higher numeric ratings indicate greater satisfaction). The rating on the P-QLES-Q Total Score (sum of Items 1 to 14) indicated that on average the subjects' quality of life, enjoyment, and

satisfaction were generally maintained from baseline (51.51) to the last visit (53.80) with continued long-term treatment of open-label aripiprazole (mean change from baseline was 2.29 [n = 79]). Mean changes from baseline were minimal at each scheduled visit (range: maximum increase of 2.49 at Month 18 [n = 55] to a maximum decrease of -4.43 at Month 66 [n = 14]). The rating on the P-QLES-Q Overall Score (Item 15) indicated that, on average, the subjects' overall quality of life was maintained as fair to good from baseline (3.90) to the last visit (3.94)(mean change from baseline was 0.04 [n = 82]). Mean changes from baseline on the PQLES-Q Overall Score were also generally minimal (range: 0.21 at Month 18 [n = 57] to −0.57 at Month 66 [n = 14]).

Safety Results:

Exposure: The average daily dose of open-label aripiprazole during the trial was 17.1 mg (ranging from 5 to 30 mg). The percentage of subjects exposed to trial medication for the longest possible duration (up to 67 months [2030 days]) was 15.3% (13/85 subjects), at an average daily dose of 18.3 mg. Cumulative exposure to aripiprazole over the duration of the trial was 205 subject years. This exposure is in addition to the 26 to 32 weeks of exposure to aripiprazole received in the previous trials (Trial 31-03-239 and Trial 31-03-241).

Adverse Events: Overall, 61/85 subjects (71.8%) experienced a total of 223 TEAEs during the trial. The percentage of subjects who experienced at least one TEAE was relatively balanced between genders (71.4% for females and 72.1% for males). The majority of all TEAEs were either mild or moderate; 6/85 subjects (7.1%) experienced at least one severe TEAE. The most frequently reported TEAEs (incidence ≥ 5% in the total population) by decreasing frequency were headache (13/85 subjects, 15.3%), influenza and increased weight (each 9/85 subjects, 10.6%), pyrexia (8/95 subjects, 9.4%), vomiting and pain (each 7/85 subjects, 8.2%), nasopharyngitis (6/85 subjects, 7.1%), and nausea, decreased appetite, somnolence, anxiety, and cough (each 5/85 subjects, 5.9%).

The most frequently reported potentially drug-related TEAEs (incidence of ≥ 3% of subjects overall) were increased weight (8/85 subjects, 9.4%), somnolence (4/85 subjects, 4.7%), and nausea, decreased appetite, headache, and tremor (each 3/85 subjects, 3.5%). One death, attributed to a serious event of bacterial pneumonia, was reported in this trial. The fatal event was considered severe and unrelated to trial medication. The subject had received 1546 days of trial medication (30 mg/day aripiprazole) at onset of the event. Eleven (of 85) subjects (12.9%) experienced at least one treatment-emergent SAE during the trial.

Eleven (of 85) subjects (12.9%) experienced at least one treatment-emergent SAE during the trial. Treatment-emergent SAEs reported in more than one subject included suicide attempt (3/85 subjects, 3.5%) and schizophrenia (2/85 subjects, 2.4%). The following SAEs were reported by 1 subject each: bacterial pneumonia, ligament rupture, psychomotor hyperactivity, aggression, impulsive behavior, psychotic disorder, and social stay hospitalization. Six of the 11 subjects experienced a treatment-emergent SAE

that led to discontinuation of trial medication. Seven (of 85) subjects (8.2%) discontinued trial medication due to at least one TEAE. Suicide attempt was the only TEAE that led to discontinuation in more than one subject (2/85 subjects, 2.4%). All TEAEs that led to discontinuation of trial medication were categorized by the investigator as either moderate (schizophrenia and 1 event of suicide attempt) or severe (bacterial pneumonia, aggression, psychotic disorder, hypertension, and 1 event of suicide attempt).

Adverse events of special interest were summarized for the trial. Ten (of 85) subjects (11.8%) experienced at least one treatment-emergent EPS-related AE during the trial. Tremor and muscle rigidity were the only EPS-related AEs reported in more than one subject. One EPS-related AE was considered serious (psychomotor activity). Four subjects experienced a suicide-related TEAE, including 3 subjects who reported a suicide attempt and 1 subject who experienced intentional self-injury during the trial.

All 3 events of suicide attempt were considered serious; 2 of these 3 events led to discontinuation of trial medication (none were considered related to trial medication). The fourth event (intentional self-injury) was reported as a nonserious TEAE (considered mild and not likely related to trial medication). There were no TEAEs of either tardive dyskinesia or neuroleptic malignant syndrome, and no seizure-, hyperglycemia/diabetes-, or orthostatic hypotension-related TEAEs were reported during the trial. Other TEAEs of special interest reported by at least one subject included increased weight (9/85 subjects, 10.6%), decreased appetite (5/85 subjects, 5.9%), increased blood CPK (1/85 subjects, 1.2%), and abnormal behavior (1/85 subjects, 1.2%).

Pregnancy: No pregnancies were reported in female subjects enrolled in the trial. One pregnancy was reported for the female partner of male subject (the 6-month follow up call indicated that the baby was healthy with no known growth deviations).

Clinical Laboratory Results: None of the mean changes from baseline for any of the serum chemistry laboratory, hematology, or urinalysis tests were considered to be clinically significant. Potentially clinically significant increases in total bilirubin (defined as ≥ 2.0 mg/dL for ages 13 to 17 years and 18 years and older) were observed in 7/79 subjects (8.9%) and potentially clinically significant increases in total CPK (defined as > 500 U/L for ages 13 to 17 years; ≥ 3.0 x upper limit of normal [ULN] for 18 years and older) were observed in 6/79 subjects (7.6%) during the trial. Serum chemistry laboratory abnormalities that were reported as TEAEs included increased blood bilirubin (1 subject), increased blood CPK (1 subject), hyperkalaemia (1 subject), and hypercholesterolaemia, hyperlipidaemia, and hypertriglyceridaemia (1 subject). Potentially clinically significant changes in eosinophils and hematocrit (each 5/79 subjects, 6.3%) and hemoglobin (3/79 subjects, 3.8%) were also observed. No clinically relevant changes in hematology parameters were observed during long-term treatment with aripiprazole.

Overall, mean changes from baseline in serum prolactin were relatively minimal and the range of mean change was similar between males and females. Three subjects (2 male

and 1 female) had a single potentially clinically significant elevated prolactin value (defined as > 1 x ULN) at some point during the trial. The overall incidence of low prolactin levels (where low serum prolactin levels are defined as < 3 ng/mL for females and < 2 ng/mL for males) was 35.4% (28/79 subjects). The incidence of low prolactin levels was greater in males (18/40 subjects, 45.0%) compared to females (10/39 subjects, 25.6%).

Vital Sign Parameters: None of the mean changes from baseline for any of the vital sign parameters were considered to be clinically significant. The most common potentially clinically significant vital sign abnormalities (incidence ≥ 5% of all subjects) included increases in standing systolic blood pressure and supine and standing diastolic blood pressure (each observed in 5/84 subjects, 6.0%). No clinically significant orthostatic changes in blood pressure were observed. One subject experienced a clinically significant increase in blood pressure that was reported as a severe TEAE of hypertension (onset on Day 1095) that led to discontinuation from trial medication.

Electrocardiogram Evaluation: No clinically meaningful changes in any ECG parameters were observed. Nine (of 82) subjects (11.0%) experienced a potentially clinically significant increase in QTcB during the trial; 3 of these 9 subjects also met the criteria for potentially clinically significant increase in QTcF. No QTc prolongations exceeded 500 msec during the trial and none were reported as TEAEs.

Other Safety Variables: Although small mean increases from baseline in waist circumference and BMI were observed with each post baseline visit, no clinically meaningful changes from baseline were observed in any of the metabolic syndrome evaluation parameters (for males or females) during the trial. Overall, no clinically meaningful trends were observed in the incidence of metabolic syndrome abnormalities between baseline and the last visit. Overall, 37/82 subjects (45.1%) had a potentially clinically significant increase in weight (≥ 7% increase compared to baseline) and 4/82 subjects (4.9%) had a potentially clinically significant decrease in weight (≥ 7% decrease compared to baseline) at the last visit of the trial. Nine (of 85) subjects (10.6%) experienced weight gain that was reported as a TEAE during the trial. Two (of 85) subjects (2.4%) experienced weight loss that was reported as a TEAE. None of the TEAEs related to change in weight led to discontinuation from the trial. Overall, mean changes from baseline to the last visit were within 0.5 SD of the general population for weight z-scores and within 1.0 SD of the general population for BMI z-scores; mean changes from baseline at each trial visit for both weight and BMI z-scores were negligible.

One subject responded ‘yes’ to an actual attempt (non-suicidal self-injurious behavior) on the suicidal behavior category of C-SSRS at the Month 66 visit. The subject’s behavior was reported as a nonserious TEAE (preferred term: intentional self-injury) on Day 1400. The event was considered mild and not likely related to trial medication.

Conclusions: Long-term administration of open-label aripiprazole (up to 67 months [2030 days]) was well-tolerated at flexible daily doses of 5 to 30 mg in adolescent and adult subjects with schizophrenia. The average daily dose of open-label aripiprazole administered during the trial was 17.1 mg. Fourteen (of 85) enrolled subjects (16.5%) completed at least 66 months (5.5 years) of treatment with open-label aripiprazole.

The incidence of subjects who discontinued from the trial due to lack of efficacy was low (3.5%) and 8.2% of subjects discontinued from the trial due to AEs.

Efficacy was maintained in adolescent or adult subjects with schizophrenia who completed the previous open-label safety and tolerability Trial 31-03-241 and continued to receive long-term treatment with flexible daily doses of 5 to 30 mg open-label aripiprazole in the current trial, as indicated by minimal changes in CGI-S score (range: −0.15 at Month 3 to a maximum change of −0.64 at Month 66). Overall, the mean change from baseline to the last visit was −0.26.

Quality of life was evaluated by the P-QLES-Q during long-term treatment of open-label aripiprazole. Quality of life, enjoyment, and satisfaction were generally maintained during long-term treatment as indicated by minimal change on P-QLES-Q Total and Overall Scores for the duration of the trial (mean changes from baseline to last visit were 2.29 and 0.04, respectively).

Long-term administration of open-label aripiprazole was generally safe and no new AEs of concern were identified. Overall, 71.8% of all subjects experienced at least one TEAE, with the majority of TEAEs reported as mild or moderate. The most frequently reported TEAEs (incidence ≤ 5% of all subjects) were headache (15.3%), influenza and increased weight (each 10.6%), pyrexia (9.4%), vomiting and pain (each 8.2%), nasopharyngitis (7.1%), and nausea, decreased appetite, somnolence, anxiety, and cough (each 5.9%).

Eleven (of 85) subjects (12.9%) experienced treatment-emergent SAEs during the trial, including one death. The death was attributed to bacterial pneumonia and was unrelated to trial medication. Treatment-emergent SAEs reported by more than one subject included suicide attempt (3 subjects) and schizophrenia (reported term: worsening of schizophrenia; 2 subjects). Seven (of 85) subjects (8.2%) discontinued trial medication due to a TEAE; all but one of the TEAEs that led to discontinuation (hypertension) was considered serious.

Ten (of 85) subjects (11.8%) experienced treatment-emergent EPS-related AEs during long-term administration of aripiprazole to adolescents and adults with schizophrenia. Tremor and muscle rigidity were the only EPS-related AEs reported in more than one subject. All EPS-related AEs were mild or moderate in severity, with exception of 1 severe event of psychomotor hyperactivity (also considered serious).

Four (of 85) subjects experienced a suicide-related TEAE, including events of suicide attempt (3 subjects) and intentional self-injury (1 subject). All 3 events of suicide attempt were considered serious, and 2 of these 3 led to discontinuation of trial medication. One subject recorded a positive response on the C-SSRS (reported as the TEAE of intentional self-injury).

There were no TEAEs related to seizure or hyperglycemia/diabetes and no individual TEAEs of tardive dyskinesia, neuroleptic malignant syndrome, or orthostatic hypotension were reported.

There were no clinically meaningful changes from baseline in serum chemistry or hematology clinical laboratory parameters during the trial. Potentially clinically significant changes in serum chemistry were limited to increases in total bilirubin (8.9%) and increases in CPK (7.6%).

Mean changes from baseline in serum prolactin were relatively minimal and relatively similar between males and females. Three (of 79) subjects (3.8%) experienced a potentially clinically significant increase in prolactin; no TEAEs related to changes in prolactin were reported. The overall incidence of low prolactin levels (defined as < 3 ng/mL for females and < 2 ng/mL for males) was 35.4% (28/79 subjects). The incidence was greater in males (18/40, 45.0%) compared to females (10/39, 25.6%). The clinical relevance of these findings is unknown in the pediatric population.

The incidence of potentially clinically significant vital sign abnormalities was low (≤ 5 subjects per parameter). No clinically significant orthostatic changes in blood pressure were observed. One subject experienced a severe TEAE of hypertension that led to discontinuation from trial medication; the event was considered not related to trial medication.

No clinically meaningful changes in QTc intervals or other ECG parameters were observed during long-term treatment with aripiprazole. Nine (of 82) subjects (11.0%) experienced a potentially clinically significant increase in QTcB during the trial.

No clinically meaningful trends were observed in the incidence of metabolic syndrome abnormalities between baseline and the last visit.

Overall, 37/82 subjects (45.1%) had a potentially clinically significant increase in weight (≥ 7% increase compared to baseline) and 4/82 subjects (4.9%) had a potentially clinically significant decrease in weight (≥ 7% decrease compared to baseline) at the last visit of the trial. Overall, mean changes from baseline to the last visit for weight and BMI z-scores were within 0.5 and 1.0 SD of the general population, respectively, and changes from baseline were negligible**.**

Report Date: 19 Dec 2012