Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597)

Clinical Summary for Protocol 31-12-293
Eudra CT No. 2012-003488-23
NCT No. 01727700

A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder

Indication:	Tourette's disorder
Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. Rockville, Maryland, United States
Trial Initiation Date:	01 Nov 2012
Trial Completion Date:	03 Sep 2013
Summary Issued:	09 Jan 2015

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

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

Protocol Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder

Trial Centers by Region: Multicenter (76 sites); Multinational (Canada, Germany, Hungary, Italy, Romania, Spain, Sweden, United States)

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

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: The purpose of this trial was to evaluate the once-daily dosing of oral aripiprazole in children and adolescents with Tourette's disorder (TD) over an 8-week treatment period. Results from one previous controlled trial (Trial 031-KOA-0703) conducted in Korea indicate that once-daily treatment with aripiprazole (administered daily up to doses of 20 mg) is efficacious in the treatment of tics in TD in children and adolescent subjects (aged 6 to 18 years).[1]

Tourette's disorder is a neuropsychiatric condition characterized by the appearance of tics that can be simple or complex in nature. A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization. Tics associated with TD become most prominent in early childhood and worsen progressively, showing the greatest tic severity at 10 years of age.[2] Depending on the number, severity, and type of tics a patient experiences, TD can have a significant adverse effect on social functioning and self-esteem during formative years that are important for social development.[3,4] Although the precise etiology of TD remains unknown, disturbances in dopaminergic and/or serotonergic pathways have been implicated because of the close association between TD and other disorders that involve imbalances in dopamine and/or serotonin (eg, obsessive-compulsive disorder [OCD] and attention deficit disorder/attention-deficit/ hyperactivity disorder [ADD/ADHD]).[5,6] Regarding such disorders, ADHD and OCD are the most prevalent comorbidities and occur in 84% of individuals with TD.[7] Aripiprazole, which exhibits partial agonism (agonism/antagonism) at dopamine D_2 and serotonin 5-hydroxytryptamine $(5\text{-HT})_{1A}$ receptors and antagonism at serotonin 5-HT_2 receptors, may therefore be of benefit to patients with TD. The currently available tablet formulation for daily administration has been investigated for the treatment of children and adolescents with tic disorders, including those with TD, in a few uncontrolled trials.[7,8,9,10,11] Limited data also indicate that aripiprazole may be efficacious in reducing tic severity in adults.[12,13,14]

Publications: None to date.

Objectives: The primary objective of the trial was to compare the efficacy of aripiprazole with placebo in the suppression of tics in children and adolescents (aged 7 to 17 years) with a diagnosis of TD. The primary efficacy measure was the change from baseline to endpoint (Week 8) on the total tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS). The key secondary efficacy measure was the Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) Change Score at endpoint (change score obtained from CGI-TS improvement scale assessment).

The secondary objective was to evaluate the safety and tolerability of aripiprazole once-daily treatment with oral tablets in children and adolescents with a diagnosis of TD.

Methodology: This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, outpatient trial designed to assess the safety and efficacy of fixed-dose oral aripiprazole once-daily tablets in children and adolescents with TD, aged 7 to 17 years at screening (the time when informed assent and consent were obtained).

After qualifying for enrollment, subjects were randomly assigned to low- or high-dose aripiprazole or placebo in a 1:1:1 ratio. For subjects who weighed < 50 kg at baseline, low and high doses of aripiprazole were 5 and 10 mg/day, respectively. For subjects who weighed ≥ 50 kg at baseline, low and high doses of aripiprazole were 10 and 20 mg/day, respectively.

All subjects randomized to the aripiprazole groups began treatment at a 2-mg/day dose, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomized dose according to a prespecified titration scheme. All subjects reached their randomized dose by Week 3 and should have remained on that randomized dose. If a subject did not tolerate the randomized dose during the titration period (before his/her first dose at Week 3), he/she was discontinued from the trial. If a subject did not tolerate the randomized dose, the dose may have been decreased one time after Week 3, to the next lower dose level or to 2 mg/day for the 5 mg/day group. Subjects who did not tolerate the reduced dose were discontinued from the trial.

The trial consisted of 2 distinct phases: a pretreatment phase and a treatment phase. The pretreatment phase consisted of a screening and washout (when applicable) period. This was followed by an 8-week treatment phase starting with the baseline visit (Day 0). There was also a follow-up period (30 ± 3 days) for subjects who discontinued from the trial or who did not roll over into the open-label trial (OPDC Protocol 31-12-294).

Subjects visited the clinic at Weeks 1, 2 (± 1 day), 4, 6, and 8 (± 3 days), at which time efficacy, safety, and outcome measures were collected. A telephone call to the subject to confirm safety and tolerability was done at Weeks 3, 5, and 7, when the clinic visit was not required. Subjects who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR) diagnostic criteria for TD, as confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) including the Diagnostic Supplement 5 (Substance

Abuse and Other Diseases, ie, Tic Disorders), and who had a TTS ≥ 20 on the YGTSS at screening and baseline (randomization), could enter into the trial once the other inclusion criteria were satisfied and no exclusion criteria had been met. Further, agreement must have been reached by the subject, a designated caregiver, and the investigator that the presenting tic symptoms impaired the subject's normal routines, based on academic achievement, occupational functioning, social activities, and/or relationships.

Number of Subjects: Approximately 126 subjects were planned for randomization in this trial from an estimated 120 sites worldwide. A total of 171 subjects were screened for the trial and 133 randomized. Of the 133 subjects randomized in the trial, 44 subjects were in the low-dose aripiprazole group (28 and 16 subjects received aripiprazole 5 and 10 mg, respectively); 45 subjects were in the high-dose aripiprazole group (30 and 15 subjects received aripiprazole 10 and 20 mg, respectively); and 44 subjects were in the placebo group. The enrollment distribution of the 133 randomized subjects across the 8 countries and 76 sites that participated in the trial was as follows: Canada (27 subjects), Germany (0 subjects), Hungary (9 subjects), Italy (5 subjects), Romania (0 subjects), Spain (0 subjects), Sweden (0 subjects), and US (92 subjects).

Diagnosis and Main Criteria for Inclusion/Exclusion: Male or female children or adolescents between 7 and 17 years of age, inclusive, who met current DSM-IV-TR diagnostic criteria for TD (as confirmed by the K-SADS-PL, including the Diagnostic Supplement 5 [Substance Abuse and Other Diseases, ie, Tic Disorders]), had a TTS ≥ 20 on the YGTSS at screening and baseline (randomization), and who, along with his/her caregiver, and the investigator all agreed that the presenting tic symptoms caused impairment in the subject's normal routines (eg, academic achievement, occupational functioning, social activities, and/or relationships) were eligible to participate in this trial. Subjects were also eligible if they did not present with neurologic conditions that may have abnormal movements (eg, Transient Tic disorder, Huntington's disease) and if they had no history of psychotic disorder or bipolar disorder. Additionally, subjects must have been in good physical health as determined by medical history, clinical laboratory tests, electrocardiogram (ECG), and physical examinations.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: The investigational medicinal product (IMP) consisted of aripiprazole and matching placebo. Aripiprazole tablets (dose strengths of 2-, 5-, 10-, and 15-mg) were manufactured by Otsuka Pharmaceutical Co, Ltd. (Japan).

Aripiprazole was to be dosed orally once daily at approximately the same time every day and taken without regard to meals. Dosing in the morning was recommended, but dosing in the evening was allowed. The 8-week placebo-controlled treatment period included a 3-week titration period to reach the randomized dose and 5 weeks of treatment at the randomized dose of 5, 10, or 20 mg/day.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Matching aripiprazole placebo tablets were manufactured by Otsuka Pharmaceutical Co., Ltd. (Japan) and placebo was dosed orally once daily.

Duration of Treatment: The double-blind treatment period was 8 weeks.

Trial Assessments: Efficacy was assessed using the YGTSS and CGI-TS (standardized and validated instruments for measuring the severity of TD).

Safety was assessed by adverse event (AE) reporting, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), 12-lead ECG, vital signs, and physical examination.

In addition, the subject's height, body weight, waist circumference, body mass index (BMI), and hormones (serum prolactin [blinded], insulin, and thyroid-stimulating hormone [TSH]) were monitored. The Columbia Suicide Severity Rating Scale (C-SSRS) was used to assess suicidality and the risk of suicide events during the trial at every clinic visit. To assess potential extrapyramidal side effects (EPS), the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS) were used and administered at every clinic visit during treatment.

Additional scales were used to measure any increase in ADHD Inattentive and ADHD Hyperactive/Impulsive symptoms, obsessive-compulsive symptoms, oppositional defiant symptoms, depression, and anxiety symptoms. These included the Swanson, Nolan, and Pelham-IV (SNAP-IV) Rating Scale, Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), Children's Depression Rating Scale - Revised (CDRS-R), and Pediatric Anxiety Rating Scale (PARS).

Criteria for Evaluation:

Efficacy: The primary endpoint was the change from baseline to endpoint (Week 8) in the YGTSS TTS. The key secondary endpoint was the mean CGI-TS Change Score at endpoint (change score obtained from CGI-TS improvement scale assessment).

Other secondary efficacy endpoints were the mean change from baseline to endpoint in Total YGTSS Score; mean change from baseline to endpoint in CGI-TS Severity Score; response rates (clinical response was defined as >25% improvement from baseline to endpoint in the YGTSS TTS or a CGI-TS Change Score of 1 [very much improved] or 2 [much improved] at endpoint); and treatment discontinuation rates.

Safety: AEs, clinical laboratory tests (hematology, serum chemistry [including prolactin, glycosylated hemoglobin, and TSH], urinalysis, and pregnancy tests), vital signs, ECGs, AIMS, BARS, SAS, C-SSRS, SNAP-IV, CY-BOCS, CDRS-R, PARS, body weight, waist circumference, and BMI.

Pharmacokinetic/pharmacodynamic Methods: Plasma concentrations of aripiprazole and its active metabolite, dehydro-aripiprazole, were quantitated using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. Blood samples were collected during Weeks 6 and 8 visits at the same time when safety laboratory samples were collected. Plasma concentrations of aripiprazole and its metabolite, dehydro-aripiprazole, were reported and summarized using descriptive statistics. Results of pharmacogenomic testing to assess cytochrome P450 (CYP) 2D6 metabolizer status were also reported. Plasma concentration data were further analyzed as part of a population PK analysis and reported separately.

Statistical Methods:

Efficacy: Assuming 5% of subjects may have dropped out of the trial without a postbaseline efficacy evaluation, a total of 126 subjects were required for randomization (in a 1:1:1 ratio to the aripiprazole low-dose, aripiprazole high-dose, and the placebo groups [42 subjects in each of the 3 groups]) to provide at least 80% power to detect a treatment difference of -5 (common standard deviation [SD] of 8.5) between at least 1 of 2 aripiprazole dose levels and placebo in the primary endpoint. Randomization was stratified by region and weight group. The planned sample size preserved an overall alpha level of 5% (2-sided) accounting for multiplicity in testing 2 comparisons (aripiprazole low dose versus placebo and aripiprazole high dose versus placebo) of the primary outcome using the Hochberg procedure. The treatment difference of -5 was considered a clinically meaningful difference in the treatment of TD. The SD of 8.5 was assumed on the basis of reported treatment effects of oral daily aripiprazole on TD. A previous aripiprazole trial in children and adolescents showed an SD of 8.96 for change from baseline in TTS (Clinical Study Report 031-KOA-0703).

Subject samples identified for this trial included the Intent-to-Treat (ITT) Sample (ie, all subjects randomly assigned to double-blind treatment [irrespective of receiving IMP]), Per Protocol (PP) Sample (ie, ITT subjects who were protocol-compliant), and Safety Sample (ie, ITT subjects who received at least 1 dose of IMP). The primary efficacy analysis was the change from baseline to endpoint (Week 8) in YGTSS TTS using the ITT Sample. The analysis was performed using a mixed model repeated measures (MMRM) linear model with terms of treatment, region, weight group, and visit week as factors, baseline YGTSS TTS as a covariate and treatment-by-week interactions in the model. Visit week was the time variable for repeated measures. To assess the time trend of treatment effect, treatment difference for the change from baseline in YGTSS TTS was also reported at each visit.

Key secondary (CGI-TS Change Score) and other efficacy endpoints in the form of mean change from baseline (Total YGTSS Score and CGI-TS Severity Score) were compared between the aripiprazole and placebo groups using the same method as described for the primary efficacy analysis. Endpoints such as response rates and treatment discontinuation rates were summarized by descriptive statistics (frequency and percent)

and were compared between the aripiprazole and placebo groups by the Cochran-Mantel-Haenszel test adjusting for the factors of region and weight group.

Sensitivity analyses of the primary and key secondary endpoints were performed under the assumptions that the mechanism of missing data was missing not at random. To understand the impact of step-down dosing on the inference of efficacy, sensitivity analyses were also performed by analyzing subjects according to the dose to which they were stepped down (ie, Subjects stepping down to 15 mg were still analyzed as in the high-dose aripiprazole group, while subjects stepping down to 2 or 5 mg were analyzed as in the low-dose aripiprazole group.).

Pharmacokinetics/pharmacodynamics/pharmacogenomics: The PK data were summarized using descriptive statistics.

Safety: Safety endpoints were summarized by descriptive statistics using the Safety Sample.

Summary of Results:

Baseline Data, Disposition, and Demographics: Of the 133 subjects randomized in the trial, 44 subjects were in the low-dose aripiprazole group (28 and 16 subjects received aripiprazole 5 and 10 mg, respectively); 45 subjects were in the high-dose aripiprazole group (30 and 15 subjects received aripiprazole 10 and 20 mg, respectively); and 44 subjects were in the placebo group. A total of 119 subjects completed the trial (ie, completed the Week 8 Visit). Fourteen subjects prematurely discontinued from the IMP because of AEs (9 subjects; 8 of these 9 subjects discontinued from the trial), consent withdrawal (4 subjects), and protocol deviations (2 subjects).

The mean age of randomized subjects was 11.1, 11.8, and 11.6 years in the low- and high-dose aripiprazole and placebo groups, respectively. Most subjects were white: 86.4%, 86.7%, and 88.6% in the low- and high-dose aripiprazole and placebo groups, respectively. The ITT Sample included a higher percentage of males than females in each of the low- and high-dose aripiprazole and placebo groups: 81.8%, 77.8%, and 75.0%, respectively. The mean weight and BMI of randomized subjects were 44.2 kg and 19.5 kg/m$_2$, 47.4 kg and 20.3 kg/m$_2$, 47.8 kg and 20.1 kg/m$_2$, respectively, in the low- and high-dose aripiprazole and placebo groups. The baseline mean total YGTSS of randomized subjects was 61.2, 62.5, and 62.8 in the low- and high-dose aripiprazole and placebo groups, respectively. The baseline mean CGI-TS Severity Score was 4.3, 4.1, and 4.2 in the low- and high-dose aripiprazole and placebo groups, respectively.

Efficacy Results: The treatment difference between the low-dose aripiprazole and placebo groups (-6.26) was statistically significant ($p = 0.0020$) for the primary efficacy variable (change from baseline to Week 8 in YGTSS TTS); the treatment difference between the high-dose aripiprazole and placebo groups (-9.85) was also statistically significant ($p < 0.0001$), based on a mixed effect repeated measure model. The treatment

difference between the low-dose aripiprazole and placebo groups (-1.03) was statistically significant (p = 0.0001) for the key secondary efficacy variable (CGI-TS Change Score at Week 8); the treatment difference between the high-dose aripiprazole and placebo groups (-1.02) was also statistically significant (p = 0.0002), based on a mixed effect repeated measure model. Sensitivity analyses of the primary and the key secondary efficacy variables corroborated these results.

Results of other secondary efficacy measures, the Total YGTSS Score and the CGI-TS Severity Score, also corroborated the primary efficacy results. The treatment difference between the low-dose aripiprazole and placebo groups for Total YGTSS Score (-13.26) and CGI-TS Severity Score (-0.80) at Week 8 was statistically significant, p = 0.0017 and p = 0.0010, respectively. The treatment difference between the high-dose aripiprazole and placebo groups for Total YGTSS Score (-19.37) and CGI-TS Severity Score (-0.92) at Week 8 was statistically significant, p < 0.0001 and p = 0.0002, respectively.

The response ratio (95% CI) (response ratio > 1 favors aripiprazole) using OC data at Week 8 in the low- and high-dose aripiprazole groups, versus the placebo group, was 1.36 (0.98, 1.88) and 1.61 (1.20, 2.16), respectively. The response ratio for the low-dose aripiprazole group compared with the placebo group was not statistically significant; the response ratio for the high-dose aripiprazole group compared with the placebo group was statistically significant (p = 0.0014). Response was observed as early as Week 1 in both aripiprazole groups (for OC) and, except for the low-dose aripiprazole group at Week 8, was maintained throughout the trial. The discontinuation rate was statistically significantly greater in the high-dose aripiprazole group compared with the placebo group, due to the discontinuation rate of subjects who weighed < 50 kg and received aripiprazole 10 mg. Of note, 5 subjects discontinued from the trial during the titration period, receiving IMP for only 2 to 15 days.

Summary of Primary and Key Secondary Efficacy Endpoints

Variable	Aripiprazole Low Dose	Aripiprazole High Dose	Placebo
YGTSS TTS at Week 8, MMRM	N[a] = 42	N[a] = 35	N[a] = 42
LS Mean (SE)[b]	-13.35 (1.59)	-16.94 (1.61)	-7.09 (1.55)
Treatment Difference (95% CI)[b]	-6.26 (-10.18, -2.34)	-9.85 (-13.84, -5.86)	
P-value[b]	0.0020	<.0001	
CGI-TS Change Score at Week 8, MMRM	N[a] = 42	N[a] = 35	N[a] = 42
LS Mean (SE)[c]	2.12 (0.21)	2.13 (0.21)	3.15 (0.20)
Treatment Difference (95% CI)[c]	-1.03 (-1.54, -0.52)	-1.02 (-1.54, -0.49)	
P-value[c]	0.0001	0.0002	

CI = confidence interval; LS = least squares; SE = standard error.

Note: Total tic score ranged from 0 to 50 with higher score for more severe symptom (larger reduction from baseline for greater improvement.
Note: CGI Change Score (obtained from CGI-TS improvement scale) ranged from 1 to 7 with lower score for better improvement.
[a]Number of subjects with baseline and a Week-8 assessment of the given variable.
[b]Derived from a repeated measures linear model with treatment, week, treatment by week interaction, region, and weight group as fixed categorical effects; the baseline value as a fixed covariate; and week as the time variable for repeated measures.
[c]Derived from a repeated measures linear model with treatment, week, treatment by week interaction, region, and weight group as fixed categorical effects; the baseline CGI-TS Severity Score as a fixed covariate, and week as the time variable for repeated measures.

Pharmacokinetic/pharmacodynamic Results: Aripiprazole and dehydro-aripiprazole mean plasma concentrations increased with the increase in doses in pediatric subjects in this trial. The observed aripiprazole and dehydro-aripiprazole plasma concentrations across the doses administered in this trial were comparable to those observed in other pediatric trials.

Safety Results: No deaths or any other serious treatment-emergent adverse events (TEAEs) were reported during the trial. Discontinuation of IMP due to a TEAE occurred in 9 subjects: 1 subject (2.3%) each, in the low-dose aripiprazole and placebo groups and 7 subjects (15.6%) in the high-dose aripiprazole group. (Subject 530S3094 in the low-dose [5 mg] aripiprazole group was discontinued from IMP due to severe somnambulism, but completed the trial.)

Overall Summary of Adverse Events (Safety Sample)							
	Aripiprazole Low Dose			Aripiprazole High Dose			Placebo (N = 44)
Subjects	5 mg (< 50 kg) (N = 28)	10 mg (≥ 50 kg) (N = 16)	Total (N = 44)	10 mg (< 50 kg) (N = 30)	20 mg (≥ 50 kg) (N = 15)	Total (N = 45)	
Number (%) of Subjects	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to TEAE	1 (3.6)	0 (0.0)	1 (2.3)	6 (20.0)	1 (6.7)	7 (15.6)	1 (2.3)
Any TEAE	19 (67.9)	10 (62.5)	29 (65.9)	22 (73.3)	12 (80.0)	34 (75.6)	18 (40.9)

[a]Percentages were based on the number of subjects in the Safety Sample.

The overall incidence of TEAEs in the low- and high-dose aripiprazole groups was 65.9% and 75.6%, respectively, and 40.9% in the placebo group. The most frequently reported TEAEs that occurred in the low- and high-dose aripiprazole groups (with an incidence of ≥ 5% in both aripiprazole groups) were sedation (18.2% and 8.9%, respectively), somnolence (11.4% and 15.6%, respectively), increased appetite (9.1% and 6.7%, respectively), fatigue (6.8% and 15.6%), and headache, nasopharyngitis, and nausea (6.8% and 8.9%, respectively, each).

In general, TEAEs with an incidence of ≥ 5% in either aripiprazole group were experienced by a greater proportion of subjects who weighed < 50 kg than subjects who weighed ≥ 50 kg. In the low-dose aripiprazole group, the exceptions were sedation and somnolence in < 50-kg subjects (14.3% and 10.7%, respectively) versus ≥ 50-kg subjects

(25.0% and 12.5%, respectively). In the high-dose aripiprazole group, the exceptions were akathisia and headache in < 50-kg subjects (3.3% and 6.7%, respectively) versus ≥ 50-kg subjects (13.3% for each). Most TEAEs were mild or moderate in intensity in the low- and high-dose aripiprazole and placebo groups. There was 1 severe TEAE of somnambulism in the low-dose aripiprazole group; 4 severe TEAEs of lethargy, sedation, somnolence, and insomnia in the high-dose aripiprazole group; and no severe TEAEs reported in the placebo group. TEAEs considered by the investigator as potentially causally related to the IMP were reported for 20 (45.5%), 28 (62.2%), and 10 (22.7%) subjects in the low- and high-dose aripiprazole and placebo groups, respectively.

There were 1 (2.3%), 6 (13.3%), and no subjects in the low- and high-dose aripiprazole and placebo groups, respectively, who experienced EPS-related TEAEs. The treatment-difference was statistically significant only between the high-dose aripiprazole and placebo groups for the EPS rating scales of SAS ($p = 0.0357$) and AIMS ($p = 0.0382$). Weight gain-related TEAEs in the low- and high-dose aripiprazole and placebo groups were reported for 5 (11.4%), 3 (6.7%), and 1 (2.3%) subjects, respectively. There were no TEAEs related to prolactin, hyperglycemia and diabetes, lipid parameters, or overdose.

The incidence of potentially clinically relevant laboratory values was similar across the low- and high-dose aripiprazole and placebo groups, except for creatine phosphokinase (CPK) and fasting glucose, which were elevated in 2 subjects each in the low- and high-dose aripiprazole groups versus no subjects in the placebo group.

While 2 subjects noted emergent suicidal ideation and 4 subjects had worsening suicidal ideation per responses to the C-SSRS, no suicidal behavior or ideation with a specific plan was observed and no suicide related AEs were reported.

Of the safety rating scales, SNAP-IV, CY-BOCS, CDRS-R, and PARS, no statistically significant difference was observed between the aripiprazole (low and high doses) and placebo groups, except on the SNAP-IV, where high-dose aripiprazole showed significant improvement over placebo in inattention subscale score ($p = 0.0027$), hyperactivity/impulsivity subscale score ($p = 0.0352$), and ADD/ADHD subscale total score ($p = 0.0048$).

Conclusions:

- Aripiprazole was efficacious in the treatment of tics in children and adolescents (aged 7 to 17 years) with a diagnosis of TD. The improvement after administration of oral daily doses of 5 to 20 mg of aripiprazole in the primary efficacy endpoint of YGTSS TTS, was observed after the first week of treatment and was sustained through Week 8. Efficacy was robust, as demonstrated by statistically significant changes not only in the YGTSS TTS, but also in the key secondary endpoint of CGI-TS Change Score.

- Oral daily doses of 5 to 20 mg of aripiprazole were generally well tolerated in pediatric subjects with TD and no new safety findings were identified in this population.
- Aripiprazole and dehydro-aripiprazole mean plasma concentrations increased with dose in pediatric subjects in this trial and were comparable to those observed in populations receiving aripiprazole in other pediatric trials.

Report Date: 04 Dec 2013

References:

[1] Yoo HK, Joung YS, Lee JS, Song DH, Lee YS, Kim JW, Kim BN, Cho SC. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. J Clin Psychiatry. 2013 Aug;74(8):e772-e780.

[2] Leckman JF, Zhang H, Vitale A, Lahnin F, Lynch K, Bondi C, Kim YS, Peterson BS. Course of tic severity in Tourette syndrome: the first two decades. Pediatrics. 1998 Jul;102(1 Pt 1):14-9.

[3] Cutler D, Murphy T, Gilmour J, Heyman I. The quality of life of young people with Tourette syndrome. Child Care Health Dev. 2009 Jul;35(4):496-504.

[4] Golder T. Tourette Syndrome: Information for school nurses. J Sch Nurs. 2010 Feb;26(1):11-7. Epub 2009 Aug 24.

[5] Steeves TD, Fox SH. Neurological basis of serotonin-dopamine antagonists in the treatment of Gilles de la Tourette syndrome. Prog Brain Res. 2008;172:495-513.

[6] Wong DF, Brasic JR, Singer HS, Schretlen DJ, Kuwabara H, Zhou Y, Nandi A, Maris MA, Alexander M, Ye W, Rousset O, Kumar A, Szabo Z, Gjedde A, Grace AA. Mechanisms of dopaminergic and serotonergic neurotransmission in Tourette syndrome: clues from an in vivo neurochemistry study with PET. Neuropsychopharmacology. 2008 May;33(6):1239-1251.

[7] Budman C, Coffey BJ, Shechter R, Schrock M, Wieland N, Spirgel A, Simon E. Aripiprazole in children and adolescents with Tourette disorder with and without explosive outbursts. J Child Adolesc Psychopharmacol. 2008 Oct;18(5):509-15.

[8] Seo WS, Sung HM, Sea HS, Bai DS. Aripiprazole treatment of children and adolescents with Tourette disorder or chronic tic disorder. J Child Adolesc Psychopharmacol. 2008 Apr;18(2):197-205.

[9] Yoo HK, Choi SH, Park S, Wang HR, Hong JP, Kim CY. An open-label study of the efficacy and tolerability of aripiprazole for children and adolescents with tic disorders. J Clin Psychiatry. 2007 Jul;68(7):1088-1093.

[10] Murphy TK, Mutch PJ, Reid JM, Edge PJ, Storch EA, Bengtson M, Yang M. Open label aripiprazole in the treatment of youth with tic disorders. J Child Adolesc Psychopharmacol. 2009 Aug;19(4):441-447.

[11] Eddy CM, Rickards, HE, Cavanna AE. Treatment strategies for tics in Tourette syndrome. Ther Adv Neurol Disord. 2011 Jan;4(1):25-45.

[12] Kawohl W, Schneider F, Vernaleken I, Neuner I. Aripiprazole in the pharmacotherapy of Gilles de la Tourette syndrome in adult patients. World J Biol Psychiatry. 2009;10(4 Pt 3):827-31.

[13] Padala PR, Qadri SF, Madaan V. Aripiprazole for the treatment of Tourette's disorder. Prim Care Companion J Clin Psychiatry. 2005;7(6):296-299.

[14] Cui YH, Zheng Y, Yang YP, Liu L, Li J. Effectiveness and tolerability of aripiprazole in children and adolescents with Tourette’s disorder: a pilot study in China. J Child Adolesc Pyschopharmacol. 2010 Aug;20(4):291-8.