Korea Otsuka Pharmaceutical
Co., Ltd.

Aripiprazole (OPC-14597)
Clinical Summary for Protocol 031-KOA-0703
NCT No. 00706589

A Randomized, Double-blind, Dose-adjustment, Placebo-controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder

Indication:	Chronic tic disorders or Tourette's disorder
Clinical Development Phase:	3
Sponsor:	Korea Otuska Pharmaceutical Co., Ltd. Seoul, Korea
Trial Initiation Date:	18 Aug 2008
Trial Completion Date:	21 Apr 2010
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 Randomized, Double-blind, Dose-adjustment, Placebo-controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder

Trial Center(s) by Region: Multicenter (6 sites, Korea)

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

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: Aripiprazole, a Quinolinone derivative
7-[4-[4-(2,3-dichlorophenyl)-1- piperazinyl]butoxy]-3,4- dihydro-2(1H)-quinolinone) is a novel antipsychotic agent having a mode of action that differs from those of typical and atypical antipsychotic agent. Biochemically, aripiprazole is shown to be a partial agonist of D2 family of dopamine (DA) receptors. In vitro, aripiprazole showed a partial agonist profile in inhibition of prolactin release from the primary cultured anterior pituitary cell. In vivo, aripiprazole is shown to exhibit antagonist properties in an animal model of dopaminergic hyperactivity (blockade of apomorphine-induced stereotype) and agonist activity in an animal model of dopaminergic hypoactivity (blockade of increased dopamine synthesis in reserpine-treated mice and rats). Aripiprazole blocks postsynaptic D2 receptors at a dose comparable to that at which it acts as an agonist at presynaptic DA autoreceptor.

Aripiprazole was developed for the treatment of subjects with schizophrenia and other disorders characterized by the presence of psychotic symptoms, and clinical studies in subjects with bipolar mania, dementia of Alzheimer's type, depression/psychotic disorders and nonschizophrenic disorders are currently undergoing.

After the approval of aripiprazole for treatment of schizophrenia with the brand name of Abilify®, aripiprazole was approved for maintenance therapy of schizophrenia by the Food and Drug Administration in the United States on 28 Aug 2003. Aripiprazole was approved for the treatment of schizophrenia and bipolar disorder from the data of a pharmacokinetic bridging trial on 01 Aug 2002 in domestic area. Aripiprazole has not been approved for treatment of chronic tic disorders and Tourette's disorder in any marketed countries.

This trial examined the efficacy and safety of aripiprazole treatment in children and adolescents with chronic tic disorders or Tourette's disorder and provided medical opportunity to the children and adolescents who participated in the this trial and who were suffering from these diseases.

Publications: 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):e772-80.

Objectives:

Primary objective:

To demonstrate the efficacy of aripiprazole versus placebo in children and adolescents with chronic tic disorders or Tourette's disorder using mean change from randomization to the final visit in Total Tic Scores (TTS) assessed by the Korean version of the Yale Global Tic Severity Scale (K-YGTSS).

Secondary objectives:

1) To assess the response rate and partial response rate of treatment with aripiprazole compared to placebo as measured by the Tourette's syndrome-Clinical Global Impression – Improvement (TS-CGI-I) scale.
2) To assess the efficacy of treatment with aripiprazole compared to placebo by measuring the mean change in Tourette's syndrome-Clinical Global Impression – Severity (TS-CGI-S) of illness scale.
3) To assess the safety and tolerability of treatment with aripiprazole compared to placebo in children and adolescents.

Methodology: This was a randomized, double-blind, dose-adjustment, placebo-controlled trial to evaluate the efficacy and safety of aripiprazole in children and adolescents with chronic tic disorders or Tourette's disorder. Subjects who were given sufficient explanation, signed the informed consent form, underwent screening procedures, and satisfied all the inclusion/exclusion criteria were randomized to either aripiprazole or placebo and were administered the investigational medicinal product (IMP) for 10 weeks. An appropriate dose (2 mg to 20 mg) of aripiprazole, or placebo of identical dosage forms, was administered daily at about the same time (if possible, in the morning) and without regard to meals.

Number of Subjects:

Planned:	Entered/Randomized: Total: 56 (28 subjects per treatment group accounting for drop-out rate of 25%)
Actual:	Entered/Randomized: Total 61
Aripiprazole:	Entered/Randomized: 32; Treated: 31; Analyzed: 32 (intention-to-treat [ITT]), 31 (full analysis set [FAS]), 23 (per protocol [PP])
Placebo:	Entered/Randomized: 29; Treated: 29; Analyzed: 29 (ITT), 29 (FAS), 21 (PP)

Diagnosis and Main Criteria for Inclusion/Exclusion: Subjects were male or female, 6 to 18 years of age, diagnosed with chronic tic disorders (vocal tic and motor tic) or Tourette's disorder according to Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) (using the Kiddie-Schedule for Affective Disorders and

Schizophrenia, Present and Lifetime Version – Korean version [K-SADS-PL-K]) with requiring drug therapy, and ≥22 TTS on the K-YGTSS at the baseline visit (Visit 2).

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Aripiprazole, 2 mg, 5 mg, 10 mg, 15 mg, administered orally, once daily.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration: placebo, administered orally, once daily.

Duration of Treatment and Administration Method: Eligible subjects (based on the inclusion/exclusion criteria) were randomized to either aripiprazole or placebo of identical dosage form on Day 1 and were administered the IMPs for 10 weeks.

All subjects visited the hospital every 2 weeks, and the investigator adjusted the IP dose according to the improvement of tic symptoms and incidence of adverse events.

The dose increase schedule was from 2 mg/day to 5 mg/day, 10 mg/day, 15 mg/day, and 20 mg/day, and the decision to increase the dose to the next highest dose was made every 2 weeks. The maximum target dose was 20 mg/day, but it was not mandatory to reach the maximum dose. The investigator made a final decision on the dose adjustment based on the improvement of tic symptoms (TS-CGI-I scale score) and AEs according to the following criteria:

- Criteria for maintaining dose: a score of 1 or 2 on the TS-CGI-I scale and tolerable AE.
- Criteria for increasing dose: a score of ≥3 on the TS-CGI-I scale and tolerable AE.
- Criteria for reducing dose: in the event of an intolerable adverse event(s), the dose could be decreased to the previous dose or the IP could be discontinued based on the investigator's discretion.

If the dose was decreased to the previous dose, the reduced dose was maintained until the final visit.

Trial Assessments:
Efficacy: K-YGTSS, TS-CGI-I, and the Tourette's syndrome-Clinical Global Impression – Severity (TS-CGI-S) scale.

Safety: adverse events (AEs), extrapyramidal symptoms (EPS) (Simpson-Angus Rating Scale [SARS], Barnes-Akathisia Rating Scale [BARS], and Abnormal Involuntary Movement Scale [AIMS]), vital signs, clinical laboratory tests, serum prolactin concentration, electrocardiograms (ECGs), physical examination, and change in weight, body mass index (BMI), and waist circumference.

Criteria for Evaluation:
Efficacy:

Primary efficacy outcome measures:
Mean change of TTS in K-YGTSS from randomization (Baseline, Visit 2) to the final visit (Visit 7).

Secondary efficacy outcome measures:

1. Percent change of TTS in the K-YGTSS from randomization to the final visit.
2. Response rate (percentage of subjects with 1 or 2 score) and partial response rate (percentage of subjects with 3 score) in TS-CGI-I scale at final visit.
3. Mean change of TS-CGI-S scores from randomization to the final visit.

Safety:

Safety outcome measures:

1. Adverse events and withdrawal from the trial due to AEs.
2. Extrapyramidal symptoms: Mean change from randomization to the final visit in scores on the SARS, Global Clinical Assessment of Akathisia from BARS, and AIMS.
3. Change in values on vital signs (blood pressure and pulse in a sitting position), clinical laboratory tests, serum prolactin concentration, 12-lead ECGs, and physical examination from randomization to the final visit.
4. Percentage of subjects showing significant weight change: significant weight gain or weight loss (significant weight change was defined as ≥7% weight gain or loss of baseline weight) from randomization to the final visit.
5. Change in BMI and waist circumference from randomization to the final visit.

Statistical Methods:
Efficacy:

Primary efficacy outcome measures: The descriptive statistics for TTS were presented for Baseline, the final visit, and the change from Baseline to the final visit by treatment group. Two-sample t-test was used to evaluate difference of change of TTS from Baseline to the final visit between treatment groups.

Secondary efficacy outcome measures:

1. The descriptive statistics for TTS were presented for values at each visit and the percent change from Baseline to the final visit by treatment group. One-sample t-test was used to test the mean percent change from Baseline to the final visit in each treatment group, and two-sample t-test was used to evaluate difference of percent change of TTS from Baseline to the final visit between treatment groups.
2. Response rate and partial response rate in TS-CGI-I at the final visit were summarized by treatment group. Fisher's exact test was used to evaluate the difference of response rate and partial response rate between the treatment groups.

3. The descriptive statistics for TS-CGI-S score were presented for values at each visit and the mean change from Baseline to the final visit by treatment group. Wilcoxon signed rank test was used to evaluate the difference of TS-CGI-S score between Baseline and final visit in each treatment group, and Wilcoxon rank sum test was used to evaluate difference of change of TS-CGI-S score between the treatment groups.

Safety:
Safety outcome measures:

1. The number and percentage of subjects with treatment-emergent adverse events (TEAEs) were summarized by treatment group. The percentage and 95% confidence interval (CI) of subjects who experienced one or more TEAE(s) were produced. Chi-square test was used to compare the incidence rates of TEAEs between treatment groups. The same analyses were performed on serious TEAEs, adverse drug reactions (ADRs), and TEAEs leading to withdrawal.
2. Mean score change of SARS, Global Clinical Assessment of Akathisia from BARS, and AIMS from randomization to the final visit were descriptively analyzed. Wilcoxon rank sum test was used to evaluate the difference of change from Baseline to the final visit between treatment groups.
3. BMI and waist circumference, vital signs (blood pressure and pulse rate in a sitting position), clinical laboratory tests, serum prolactin concentration, 12-lead ECGs, physical examination findings: Paired t-test (or Wilcoxon signed rank test) of the changes in continuous variables from randomization to the final visit was assessed for each group, and two sample t-test (or Wilcoxon rank sum test) was used to compare the changes between the two groups. Categorical variables of clinical laboratory tests and physical examination findings were categorized to normal and abnormal, and McNema's test was used to evaluate the change for each group.
4. Frequency (N) and percentage (%) of the subjects who gained or lost equal to and greater than 7% (≥7%) in body weight from randomization to the final visit were presented by treatment group. Fisher's exact test was used to compare the difference between the treatment groups.

Summary of Results:

Baseline Data, Disposition, and Demographics: All randomized subjects, with the exception of one subject in the aripiprazole group who withdrew due to a protocol deviation, were treated with the IMPs. Of the 61 randomized subjects, 54 subjects (25 in the placebo group, 29 in the aripiprazole group) completed the trial and 7 subjects (4 in the placebo group, 3 in the aripiprazole group) prematurely discontinued. The disposition of trial completion status did not differ between the two groups. The reasons for discontinuations were: subject was withdrawn from participation by the investigator (3 subjects); subject withdrew consent to participate (3 subjects); and protocol deviation (1 subject).

A larger number of male subjects (53, 86.89%) were randomized compared with female subjects (8, 13.11%). Mean (±SD) demographic and baseline characteristics were as follows: age, 10.95 years (±2.72); height, 146.94 cm (±15.24); body weight, 43.92 kg (±15.98); heart rate, 83.26 beats/minute (±13.00); systolic blood pressure, 107.74 mmHg (±14.36); diastolic blood pressure, 65.92 mmHg (±9.80); and, waist circumference, 68.79 cm (±10.68).

Electrocardiogram results at screening showed that overall ECG interpretation was normal in 42 subjects (68.85%) and abnormal in 19 subjects (31.15%). No abnormal ECG finding was clinically significant. Ventricular rate was 76.82 beats/min (±13.79), RR interval was 803.84 msec (±140.13), PR interval was 137.46 msec (±22.26), QRS interval was 85.46 msec (±7.84), QT interval was 373.54 msec (±26.84), and QTc interval was 418.90 msec (±20.61) for the 61 subjects.

No statistically significant difference between treatment groups was observed in any demographic and baseline characteristics.

Efficacy Results: The ITT population was defined as all randomized subjects. The FAS population was defined as subjects who took IMP at least once and had evaluable primary efficacy data. The PP population was defined as subjects included in the FAS population who completed the trial with no major protocol violation.

All 61 subjects who were enrolled and randomized in the six trial sites were included in the ITT population; 29 in the placebo group and 32 in the aripiprazole group. Of these, 60 subjects were included in the FAS population; 29 in the placebo group and 31 in the aripiprazole group (one subject withdrew before IMP administration). The PP population included 44 subjects; 21 in the placebo group and 23 in the aripiprazole group.

As the final decision on the efficacy outcome measures was to be made on the ITT population, the analysis results of each efficacy endpoint are summarized for the ITT population.

The analysis results of the primary efficacy endpoint, mean change of TTS in K-YGTSS from randomization to the final visit showed that the mean TTS changed from 29.48 (±5.60) at Baseline to 19.86 (±9.54) at the final visit for the placebo group, showing a decrease, by -9.62 (±8.83). For the aripiprazole group, it changed from 28.34 (±5.51) at Baseline to 13.55 (±9.12) at the final visit, showing a greater decrease, by -14.97 (±8.42). The difference in the change from Baseline to the final visit between the treatment groups was statistically significant (p-value=0.0196, two-sample t-test).

Secondary efficacy endpoints included the percent change of TTS in K-YGTSS from randomization to the final visit, the response rate and partial response rate in TS-CGI-I at the final visit, and mean change of TS-CGI-S score. The analysis result of percent change of TTS in K-YGTSS from randomization to the final visit showed that the mean percent change was -33.00% (±27.83) for the placebo group and -52.86% (±27.83) for

the aripiprazole group. As for the primary efficacy endpoint result, the difference between the treatment groups was statistically significant (p-value=0.0077, two-sample t-test). The analysis result of response rate (percentage of subjects with a score of 1 or 2) on the TS-CGI-I at the final visit showed a higher response rate for the aripiprazole group as 13 subjects (44.83%) in the placebo group and 21 subjects (65.63%) in the aripiprazole group were responders. However, there was no statistically significant difference in the response rate between the treatment groups.

The analysis result of partial response rate (percentage of subjects with a score of 3) on the TS-CGI-I at the final visit showed a higher partial response rate for the aripiprazole group as 4 subjects (13.79%) in the placebo group and 6 subjects (18.75%) in the aripiprazole group were partial responders. However, there was no statistically significant difference in the partial response rate between the treatment groups.

The analysis result of mean change of the TS-CGI-S score from randomization to the final visit showed that the mean TS-CGI-S score was changed from 4.69 (±0.76) at Baseline to 3.59 (±1.27) at the final visit for the placebo group, showing a decrease, by -1.10 (±1.14). It changed from 4.50 (±0.80) at Baseline to 2.81 (±1.35) at the final visit for the aripiprazole group, showing a greater decrease, by - 1.71 (±1.30). The difference in the change from Baseline to the final visit between the treatment groups was statistically significant (p-value=0.0321, Wilcoxon rank sum test).

In conclusion, the primary efficacy endpoint, mean change of TTS in K-YGTSS, and two secondary efficacy endpoints, the percent change of TTS in K-YGTSS and mean change of TS-CGI-S score from randomization to the final visit showed a statistically significant difference between the placebo group and the aripiprazole group, with aripiprazole superior to placebo. It was confirmed from the results above that aripiprazole is an effective treatment drug for chronic tic disorders or Tourette's disorder in children and adolescents.

Safety Results: A total of 60 subjects were included in the safety analysis; 28 in the placebo group and 32 in the aripiprazole group. Twenty subjects (71.43%) reported TEAEs in the placebo group, and 24 subjects (75.00%) reported TEAEs in the aripiprazole group. There was no statistically significant difference in the incidence rate of TEAEs between the treatment groups. Adverse drug reactions occurred in 14 subjects (50.00%) in the placebo group, and 15 subjects (46.88%) in the aripiprazole group. There was no statistically significant difference in the incidence rate of ADRs between the treatment groups. Neither serious TEAEs (SAEs) nor TEAEs that led to withdrawal were reported during the trial. The most common TEAEs were akathisia [4 subjects (14.29%, 5 events)] and dizziness [4 subjects (14.29%, 4 events)] in the placebo group, and nausea (6 subjects [18.75%, 6 events)] and headache [5 subjects (15.63%, 5 events)] followed by sedation [4 subjects (12.50%, 5 events)], somnolence [4 subjects (12.50%, 5 events)] and nasopharyngitis [4 subjects (12.50%, 4 events)] in the aripiprazole group. No TEAE was reported as severe. Seven TEAEs in the placebo group and 4 TEAEs in the aripiprazole group were moderate, and the rest of the TEAEs were mild. The most

common ADRs were akathisia [4 subjects (14.29%, 5 events)], followed by insomnia [3 subjects (10.71%, 4 events)], sedation [3 subjects (10.71%, 3 events)] and dizziness [3 subjects (10.71%, 3 events)] in the placebo group, and sedation [4 subjects (12.50%, 5 events)] and nausea [4 subjects (12.50%, 4 events)] followed by extrapyramidal disorder [3 subjects (9.38%, 3 events)], headache [3 subjects (9.38%, 3 events)] and somnolence [3 subjects (9.38%, 3 events)] in the aripiprazole group. (Note: ADRs with incidences of 2 subjects or less in each treatment group are not described here). Five TEAEs that occurred in the placebo group and 3 TEAEs in the aripiprazole group were moderate ADRs, and the rest were mild.

Any change from baseline to the final visit in EPS (SARS, AIMS, and BARS) was not statistically significant between the treatment groups. There were no other significant findings in the safety measures including laboratory tests, vital signs, physical examinations and 12-lead ECG.

Conclusions: On the basis of the above efficacy and safety results, aripiprazole was determined to be an effective and safe treatment medication for chronic tic disorders or Tourette's disorder in children and adolescents.

Report Date: 17 Dec 2010

Supplemental Report:
While a total of 61 subjects were randomly assigned in this clinical trial, 5 subjects (registered in addition to the 56 subjects originally planned), were excluded from additional analyses of efficacy and safety to complete a Supplemental Report. Furthermore, a newly defined analysis group, the Modified FAS, was used for the main analyses of efficacy and safety presented in the Supplemental Report.

The Modified FAS did not include 2 subjects who did not meet major inclusion criteria (past history of taking aripiprazole) and the 1 subject who did not take the IMP. A total of 53 subjects, 26 subjects in the placebo group and 27 subjects in the aripiprazole group, comprised the Modified FAS analysis group.

The efficacy and safety results from this supplementary analysis did not show any significant difference from the results obtained from the analyses performed on all of the randomly assigned subjects.

In the Modified FAS analysis group, the mean change of TTS in K-YGTSS from randomization to the final visit (primary efficacy outcome measure), the percentage change of TTS in K-YGTSS from randomization to the final visit (secondary efficacy outcome measure), and the mean change in the TS-CGI-S from randomization to the final visit (secondary efficacy outcome measure) demonstrated statistically significant differences between the treatment groups favoring aripiprazole. Although the response rate for TS-CGI-I at the final visit was not statistically significant, the response rate in the aripiprazole group was higher than in the placebo group.

The ADRs that occurred in the safety analysis group that occurred in 5% or more subjects in the aripiprazole group were; nausea [4 subjects (14.29%)], sedation [3 subjects (10.71%)], extrapyramidal disorder [3 subjects (10.71%)], headache [3 subjects (10.71%)], somnolence [3 subjects (10.71%)], anorexia [2 subjects (7.14%)] and electrocardiogram QT prolonged [2 subjects (7.14%)].

Four subjects (14.29%) were reported to have developed ADRs of extrapyramidal symptoms (akathisia, dystonia, and dyskinesia) including extrapyramidal disorder; this outcome was the same as the existing results.

In the supplementary analysis, a mean weight gain of 1.73 kg (±1.96) was reported in the aripiprazole group and it was slightly increased when compared with the existing analysis results of 1.62 kg (±2.02). However, weight gain was also observed in other aripiprazole studies in children and adolescents and the weight gain was found to be relatively lower compared to other atypical antipsychotic medications.

In this supplement analysis and other clinical studies, the serum prolactin values were significantly lowered due to the use of aripiprazole but the outcome was not clinically significant.

With respect to EPS assessed by using SARS, AIMS and BARS, the difference between the aripiprazole group and the placebo group was not statistically significant.

Based upon the analysis data obtained from all existing subjects randomly assigned and also the results of the supplement analysis that excluded the 5 additionally enrolled subjects, aripiprazole was found to be safe and effective treatment drug for children and adolescents with tic disorder and Tourette’s disorder.

Date of Supplemental Report: 30 Aug 2011