Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597)

# Clinical Summary for Protocol 31-09-268

An Open-label, Multi-center, Two Phase, Sequential Design, Single and Multiple Dose Study to Assess the Safety, Tolerability, and Pharmacokinetic Profile of an Extended Release Once-weekly Oral Formulation and an Enteric Coated Extended Release Once-weekly Oral Formulation of Aripiprazole Administered to Children and Adolescents with Tourette's Disorder

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|---|---|
| Indication: | Tourette's Disorder |
| Clinical Development Phase: | 1 |
| Sponsor: | Otsuka Pharmaceutical Development & Commercialization, Inc.<br>Rockville, Maryland, United States |
| Trial Initiation Date: | 09 Jun 2010 |
| Trial Completion Date: | 20 May 2011 |
| 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:** An Open-label, Multi-center, Two Phase, Sequential Design, Single and Multiple Dose Study to Assess the Safety, Tolerability, and Pharmacokinetic Profile of an Extended Release Once-weekly Oral Formulation and an Enteric Coated Extended Release Once-weekly Oral Formulation of Aripiprazole Administered to Children and Adolescents with Tourette's Disorder

**Trial Centers by Region:** Multicenter (13 centers; United States)

**Clinical Phase/Trial Type:** 1/Open-label, Multi-center, Safety and Tolerability

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

**Scientific Background and Explanation of Rationale:**
Tourette's Disorder (TD) is a neuropsychiatric condition characterized by the appearance of tics that can be simple or complex in nature. Although the precise etiology of TD remains unknown, disturbances in serotonergic and/or dopaminergic pathways have been implicated because of the close association of TD and other disorders that involve imbalances in serotonin and/or dopamine (eg, obsessive compulsive disorder [OCD] and attention-deficit hyperactivity disorder [ADHD]).[1,2] Aripiprazole, which exhibits partial agonism (agonism/antagonism) at dopamine $D_2$ and serotonin 5-$HT_{1A}$ receptors and antagonism at serotonin 5-$HT^2$ receptors, may therefore be of benefit for patients with TD.

The currently approved formulations of aripiprazole are intended for daily administration. A once-weekly formulation of aripiprazole has been developed for evaluation in children and adolescents in the target age range of 7 to 17 years (inclusive). Since the emergence and severity of breakthrough tics may be associated with fluctuations in dopamine tone (eg, diurnal variation, stressful situations, caffeine usage, etc), a once-weekly aripiprazole formulation was anticipated to provide adequately sustained plasma levels to minimize disturbance in dopaminergic tone over weekly dosing intervals. In addition, a once-weekly formulation was proposed to provide a more convenient dosing option for patients with TD and their caregivers, and ultimately to limit compliance-related relapse. The formulations that were investigated in this trial were extended release (ER) and enteric coated extended release (ECER) oral tablets of aripiprazole. The ECER formulation studied in this trial had the same tablet core as the ER formulation with the addition of an enteric coating.

The age range for the subject population in this trial, 7 to 17 years (inclusive), was based on published data, which reported that the onset of tics associated with TD become most prominent in early childhood and worsen progressively, showing the greatest tic severity at approximately 10 years of age.[3]
The goal of this trial was to obtain safety and tolerability data and pharmacokinetic (PK) profiles of two dose strengths of aripiprazole ER formulation and three dose strengths of

aripiprazole ECER formulation in children and adolescents with TD after single and multiple once-weekly administration.

**Publications:** None to date.

**Objectives:** The primary objectives of this trial were the following:

- Safety and tolerability: To determine the safety and tolerability of oral once-weekly ER and ECER tablet formulations of aripiprazole after single and multiple weekly dose administration.
- Pharmacokinetics (PK): To determine the PK profile of aripiprazole and its metabolite, dehydro-aripiprazole, in plasma after single- and multiple-dose administration of once-weekly ER and ECER formulations of aripiprazole in the fasted state and to determine the PK profile of aripiprazole and dehydro-aripiprazole in plasma after single dose administration after a high-fat meal.

The secondary objective of this trial was efficacy. The objective of the efficacy analysis was to explore the change from baseline in the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS) and Clinical Global Impression-Severity of Illness Scale (CGI-S) to Day 8 and Day 15 for each of the five assigned treatments. In addition, the mean change from baseline (Day 1) to Day 29/Early Termination (ET) in YGTSS-TTS and CGI-S was examined for each dose after multiple dosing.

**Methodology:** This was an open-label, multi-center, sequential design, single and multiple dose trial to assess the safety, tolerability, and PK profile of once-weekly oral ER and ECER formulation of aripiprazole administered to children and adolescents with TD. The trial consisted of two phases that evaluated the food effect on a single dose (Phase A) and the effects of multiple dosing (Phase B).

Subjects underwent screening to determine their eligibility to enter the trial. Eligible subjects were 7 to 17 years of age, inclusive, and met current DSM-IV-TR diagnostic criteria for TD. In addition, subjects were assessed to determine their ability to metabolize CYP2D6; poor metabolizers were excluded from Phase A.

Phase A of the trial assessed the safety, tolerability, and PK profile of two dose strengths of the ER formulation (27.5 and 52.5 mg) and three dose strengths of the ECER formulation (52.5, 77.5, and 110 mg) of aripiprazole under fasted and fed conditions. Each dose strength was administered first (Day 1) under fasting and then (Day 8) under fed conditions (ie, within 30 minutes after the start of a United States Food and Drug Administration-recommended high-fat meal) to evaluate the effect of food on PK profiles, safety, and tolerability of aripiprazole. Six subjects were assigned to each treatment cohort. Initially, only two subjects in a particular cohort were dosed in the fasted state. If there were no clinically significant safety or tolerability events observed or reported within 48 hours after dosing of the first two subjects, then the remaining four subjects in the cohort were dosed in a fasted state. A decision to advance to the next

cohort was made after all six subjects had received their dose (fasted state), and after the final subject had demonstrated no clinically meaningful adverse events (AEs) at the 48-hour assessment.

Phase B of the trial assessed the PK profile, safety, and tolerability of once-weekly administration of the ER (27.5 and 52.5 mg) and ECER (77.5 and 110 mg) formulations for 4 consecutive weeks. Doses were administered on Days 1, 8, 15, and 22. Ten subjects were to be assigned to each treatment cohort. Subjects who continued into Phase B after completion of Phase A in the 27.5 and 52.5 mg ER cohorts and the 77.5 and 110 mg ECER cohorts entered on Day 15 and therefore only received the last two doses scheduled (Days 15 and 22). Those doses were the same dose strength as that received during Phase A. Subjects who continued into Phase B after completion of Phase A in the 52.5 mg ECER cohort entered Phase B as "de novo" subjects on Day 1 and received all four doses scheduled (Days 1, 8, 15, and 22). Those doses were at the dose strength of the Phase B cohort enrolling at the time of roll-over. Subjects may also have entered Phase B of the trial without participating in Phase A.

Cohort Safety Review meetings were held to assess safety and tolerability at 48 hours and 6 days after each subject was dosed and at ad hoc meetings, as necessary.

**Number of Subjects:** The expected number of subjects planned for this trial was 40. Phase A: 30 subjects and Phase B: 40 subjects (30 subjects were expected to continue from Phase A into Phase B). Subjects were replaced to assure that the appropriate number of subjects completed each phase of the trial.

A total of 69 subjects were screened for enrollment into the trial, and 46 unique subjects were enrolled, all of whom were included in the safety and efficacy analyses.
Five subjects participated in Phase A only, 13 subjects participated in Phase B only, and 28 subjects participated in both Phases A and B.

**Diagnosis and Main Criteria for Inclusion/Exclusion:** Subjects must have been 7 to17 years old, inclusive, and had a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-text revision (DSM-IV-TR) diagnosis of TD.

**Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration:** Two ER dose strengths of an aripiprazole tablet formulation were used in this trial: ER tablet 27.5 mg-A and ER tablet 52.5 mg-A. In addition, three ECER dose strengths of an aripiprazole tablet formulation were used in this trial: ECER tablet 52.5 mg-A; ECER tablet 77.5 mg-A; and ECER tablet 110 mg-A.

Note: Originally, only the ER formulation, at dose strengths of 27.5, 52.5, 77.5, and 110 mg, was planned to be used in this trial. Amendment 1 of the protocol added the ECER formulation at a dose strength of 52.5 mg and the option of switching the 77.5 and 110 mg doses from the ER formulation to the ECER.

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

**Duration of Treatment:** Individual subject duration varied depending on the number of phases in which a subject participated. For subjects who participated in both phases, participation ranged from approximately 81 to 136 days (including 7 to 60 days for screening and washout, 15 days for Phase A, 29 days for Phase B, and 30 [+ 2] days for follow-up after the last dose of trial drug). The actual trial duration (first subject screened to last subject completed) was approximately 11.5 months.

**Trial Assessments:**

*Efficacy:* YGTSS and the CGI-S.

*Pharmakokinetics:* the area under the observed plasma concentration versus time curve, from 0 to 168 hours after dosing in Phase A (Day 1) and Phase B (Day 22) ($AUC_{0\text{-}168h}$); the area under the observed plasma concentration versus time curve, from 0 to 24 hours after dosing in Phase A (Days 1 and 8, Phase A) ($AUC_{0\text{-}24h}$); maximum observed plasma concentration (measured for the full profile and also between 0 to 24 hours for Day 1 of Phase A) ($C_{max}$); time of the maximum observed plasma concentration ($t_{max}$); observed plasma concentration at 168 hours after dosing in Phase A (Day 1) and Phase B (Day 22) ($C_{168h}$); apparent terminal elimination rate constant calculated by log-linear regression of terminal log-linear segment of the plasma concentration-time curve, Phase A (Day 1) and Phase B (Day 22) only ($\lambda_z$); Apparent terminal elimination half-life, calculated as $t_{1/2} = \ln(2)/\lambda_z$, Phase A (Day 1) and Phase B (Day 22) only ($t_{1/2}$); and apparent clearance of aripiprazole (only in Phase A Day 1) from plasma after oral administration ($Dose/AUC_{inf}$) (CL/F).

*Safety:* AEs, clinical laboratory tests (serum chemistry, hematology, and urinalysis), physical examination, vital signs, electrocardiograms (ECGs), Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and the Columbia-Suicide Severity Rating Scale (C-SSRS).
Other: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL), Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), Pediatric Anxiety Rating Scale (PARS), Children's Depression Rating Scale (CDRS-R), and the Conners' Parent Rating Scale-Revised: Short Version (CPRS-R:S).

**Criteria for Evaluation:**

*Primary Outcome Variables:*

- Safety: Reported AEs, vital signs (blood pressure, orthostatic reaction, and heart rate), electrocardiograms, clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, extrapyramidal symptoms (EPS), and C-SSRS scores. Other safety variables included the PARS, CDRS-R, and CPRS-R:S scores.

- Pharmacokinetics: Maximum (peak) plasma concentration ($C_{max}$), plasma concentration at 168 hours after dosing ($C_{168h}$), area under the concentration-time curve from time zero to 168 hours after dosing (zero to 24 hours for the fed state), ($AUC_{0-168h}$, $AUC_{0-24h}$), time to maximum (peak) plasma concentration ($t_{max}$) and terminal-phase elimination half-life ($t_{1/2,z}$) for aripiprazole and dehydro-aripiprazole; and apparent clearance of aripiprazole from plasma after oral administration (CL/F).

*Secondary Outcome Variables:* Efficacy analysis was exploratory. For Phase A of the trial, summary statistics were provided for the change from baseline in YGTSS-TTS and CGI-S to Day 8 and Day 15 for each of the five assigned treatments (27.5 and 52.5 mg of the aripiprazole ER formulation and 52.5, 77.5, and 110 mg of the aripiprazole ECER formulation). Mean change from baseline (Day 1 of Phase B) to Day 29/ET in YGTSS-TTS and CGI-S was also calculated for each dose examined in Phase B.

**Pharmacokinetic/pharmacodynamic Methods:**

*Bioanalytical:* Plasma concentrations of aripiprazole and dehydro-aripiprazole were determined using high-performance liquid chromatography with tandem mass spectrometry (HPLC−MS/MS).

*Pharmacokinetics:* Plasma concentrations for aripiprazole and dehydro-aripiprazole were analyzed by noncompartmental methods. The following variables were determined: peak plasma concentration of the profile ($C_{max}$), the area under the observed plasma concentration versus time curve from 0 to 24 hours ($AUC_{0-24}$) and 0 to 168 hours ($AUC_{0-168}$) after dosing, time of the maximum observed plasma concentration ($t_{max}$), and apparent terminal elimination half-life. Apparent clearance (CL/F) of aripiprazole from plasma after oral administration was determined along with fed/fasted ratios of $C_{max}$ and $AUC_{0-24}$ (Day 8/Day 1) in Phase A. The in vivo release profiles for the various formulations after single-dose administration under fasting conditions were determined by deconvolution methodology.

*Statistics:* Plasma concentration and PK data for aripiprazole and dehydro-aripiprazole were summarized with descriptive statistics by analyte and treatment group.

**Statistical Methods:** In the PK analysis, only subjects who had complete PK profiles were included. In the efficacy analysis, all enrolled subjects in each phase of the trial who took at least one dose of trial drug during that phase with baseline and at least one postbaseline efficacy assessments for the respective phase were included for analysis for that phase. In the safety analysis of each trial phase, all enrolled subjects who took at least one dose of the respective phase's trial drug were included. Descriptive statistics, including mean, standard deviation, median, minimum, and maximum, and number and percentage of subjects were used to summarize results from the safety and efficacy analyses as appropriate.

**Summary of Results:**

**Baseline Data, Disposition, and Demographics:**
A total of 69 subjects were screened for enrollment into the trial, and 46 unique subjects were enrolled: 5 subjects participated in Phase A only, 13 subjects participated in Phase B only, and 28 subjects participated in both Phases A and B.

During Phase A, 2 subjects (6.1%) discontinued from the trial: 1 subject in the 110 mg ECER cohort and 1 subject in the 52.5 mg ECER cohort. Both of these subjects withdrew consent.

Of the 31 subjects (93.9%) who completed Phase A, 22 subjects (66.7%) rolled over into Phase B at the dose level they had received during Phase A and 6 subjects (18.2%) who had received 52.5 mg ECER during Phase A entered Phase B as de novo subjects at the dose level currently enrolling. Thirteen subjects were enrolled into Phase B without completing Phase A. Of the 41 subjects who participated in Phase B, 4 subjects (9.8%) discontinued from the trial. Two subjects in the 27.5 mg ER cohort (1 de novo and 1 rollover) withdrew consent, 1 de novo subject in the 110 mg ECER cohort withdrew consent, and 1 de novo subject in the 110 mg ECER cohort withdrew because of an AE.

The majority of subjects who participated in Phase A were male (23 of 33 subjects). Most subjects were white (70.0%) and most were not Hispanic or Latino (73.0%). Mean (SD) age was 12.91 years (2.85 years); age of the subjects ranged from 8 to 17 years. Mean (SD) weight and body mass index (BMI) were 54.20 kg (18.78 kg) and 21.32 $kg/m^2$ (4.71 $kg/m^2$).

The majority of the 41 subjects participating in Phase B were male (31 subjects), most subjects were white (73.0%), and most were not Hispanic or Latino (66.0%). Mean (SD) age was 12.83 years (2.69 years); age of the subjects ranged from 8 to 17 years. Mean (SD) weight and BMI were 53.02 kg (15.78 kg) and 20.71 $kg/m^2$ (3.50 $kg/m^2$), respectively.

Overall, the mean (SD) time since onset for TD for subjects enrolled in Phase A was 5.22 years (3.32 years), with a mean (SD) time since diagnosis of TD of 2.88 years (3.09 years). A total of 16 subjects also had concurrent ADHD and two subjects had concurrent OCD (CY-BOCS score $\leq$ 20). The mean (SD) TTS (ie, the sum of the total motor and vocal tic severity scores; maximum score of 50) was 30.94 (5.70). The mean (SD) YGTSS (ie, the sum of the TTS and the YGTSS ranking of impairment; maximum score of 100) was 62.45 (11.92).

Subjects enrolled in Phase B had a mean (SD) time since onset for TD and a mean (SD) time since diagnosis of TD of 5.59 years (3.45 years) and 3.36 years (3.16 years), respectively. A total of 24 subjects also had concurrent ADHD and three subjects had concurrent OCD (CY-BOCS score $\leq$ 20); one of these subjects had concurrent ADHD

and OCD. The mean (SD) TTS was 29.90 (6.19). The mean (SD) YGTSS was 59.41 (11.85).

**Efficacy Results:**

- Efficacy results are presented for all enrolled subjects in each phase of the trial who took at least one dose of trial drug during that phase with baseline and at least one postbaseline efficacy assessments for the respective phase by using the last observation carried forward approach as the primary approach. Efficacy was an exploratory objective for this trial.
- During Phase A, the mean change from baseline in YGTSS-TTS increased with increasing dose at Day 8 (fasted state), and the mean change from baseline for the 52.5 mg ECER cohort was less than that of the 52.5 mg ER cohort. At Day 15 (fed state), the 52.5 mg ER cohort had the greatest mean change from baseline, closely followed by the 77.5 mg ECER cohort and the 110 mg ECER cohort. The mean change from baseline for the 52.5 mg ECER cohort was similar to that of the 27.5 mg ER cohort.
- Overall, during Phase B, the 27.5 and 52.5 mg ER cohorts had similar mean changes from baseline in YGTSS-TTS, except at Day 29 when the 52.5 mg ER cohort had a greater mean change from baseline compared with that of the 27.5 mg ER cohort. The 77.5 mg ECER cohort had the greatest mean change from baseline at all time points compared with that of the other cohorts. De novo subjects had greater mean changes from baseline compared with those of rollover subjects in the 27.5 mg ER and 77.5 mg ECER cohorts; the opposite was true for the 52.5 mg ER cohort, and mean changes from baseline were similar between de novo and rollover subjects in the 110 mg ECER cohort.
- During Phase A, the mean change from baseline in CGI-S was greatest at Days 8 and 15 for the 52.5 mg ER and 110 mg ECER cohorts. For the 52.5 mg ECER cohort, the mean change from baseline was similar to that of the 77.5 mg ECER cohort at Day 8, but the mean change from baseline was lower than that of the 27.5 mg ER cohort at Day 15.
- Overall, during Phase B, the mean change from baseline in CGI-S increased with increasing dose and increased from Day 8 through Day 29. The 110 mg ECER cohort had the greatest mean change from baseline at all timepoints compared with that of the other cohorts. For the 77.5 and 110 mg ECER cohorts, de novo subjects had greater mean changes from baseline compared with those of rollover subjects; the opposite trend was seen in the 27.5 and 52.5 mg ER cohorts.

**Pharmacokinetic/pharmacodynamic Results:**
Mean (SD) aripiprazole PK variables after single-dose administration of the ER and ECER aripiprazole formulations to children and adolescents with TD in the fasted state are presented below:

**Mean (SD) Aripiprazole PK Variables After Single-dose Administration of ER and ECER Formulations in the Fasted State**

| PK Variable | 27.5 mg ER (n=6) | 52.5 mg ER (n=6) | 52.5 mg ECER (n=7) | 77.5 mg ECER (n=6) | 110 mg ECER (n=7) |
|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 41.5 (11.1) | 80.9 (39.9) | 47.6 (17.3) | 123 (40.2) | 139 (62.3) |
| $t_{max}$ (h)[a] | 24.00 (3.00 – 72.00) | 24.00 (6.00 – 24.05) | 71.97 (6.08 – 72.42) | 24.04 (23.97 – 72.00) | 71.83 (23.93 – 80.22) |
| $AUC_{0-168}$ (ng • h/mL) | 3520 (1530) | 7010 (3420) | 5100 (1730) | 12900 (4460) | 13800 (5970) |
| $t_{1/2}$ (h) | 43.56 (10.94)[b] | 66.36 (34.50)[b] | 48.52 (15.56) | 71.80 (34.27)[b] | 55.76 (19.21) |
| CL/F (L/h) | 9.19 (5.03)[b] | 8.37 (3.91)[b] | 9.82 (3.38) | 5.20 (2.13)[b] | 7.93 (3.95) |
| $C_{168h}$ (ng/mL) | 6.59 (5.08) | 19.9 (16.0) | 11.3 (6.95) | 37.0 (19.3) | 35.9 (20.3) |

[a] Median (minimum-maximum).
[b] n=5.

Mean (SD) aripiprazole PK variables after administration of single-dose ER and ECER aripiprazole formulations to children and adolescents with TD in the fed state are presented below:

**Mean (SD) Aripiprazole PK Variables After Single-dose Administration of ER and ECER Formulations With a High-fat Meal**

| PK Variable | 27.5 mg ER (n=6) | 52.5 mg ER (n=6) | 52.5 mg ECER (n=7) | 77.5 mg ECER (n=6) | 110 mg ECER (n=7) |
|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 121 (53.1) | 141 (111) | 84.6 (79.3) | 136 (80.9) | 149 (83.3) |
| $AUC_{0-24}$ (ng • h/mL) | 2080 (863) | 2150 (1610) | 820 (775) | 1960 (1520) | 2080 (1120) |

Note: The $C_{max}$ is based on 0-24 hours after dosing.

Mean (SD) fed/fasted ratios for aripiprazole PK variables after administration of single-dose ER and ECER aripiprazole formulations to children and adolescents with TD are presented below:

| Mean (SD) Fed/Fasted Ratio of Aripiprazole PK Variables After Single-dose Administration of ER and ECER Formulations With a High-fat Meal | | | | | |
|---|---|---|---|---|---|
| **PK Variable** | **27.5 mg ER (n=6)** | **52.5 mg ER (n=6)** | **52.5 mg ECER (n=7)** | **77.5 mg ECER (n=6)** | **110 mg ECER (n=7)** |
| Fed/Fasted Ratio $C_{max}$ | 3.30 (1.58) | 1.60 (0.770) | 1.84 (1.32) | 1.18 (0.763) | 1.64 (0.821) |
| Fed/Fasted Ratio $AUC_{0-24}$ | 3.57 (1.71) | 1.99 (1.02) | 1.26 (1.06) | 1.25 (1.19) | 1.93 (1.07) |

Note: The $C_{max}$ for fed/fasted ratios are based on 0-24 hours after dosing.

Mean (SD) aripiprazole PK variables after multiple-dose weekly administration of the ER and ECER aripiprazole formulations are presented below:

| Mean (SD) Aripiprazole PK Variables After Multiple-dose Weekly Administration of ER and ECER Formulations | | | | |
|---|---|---|---|---|
| **PK Variable** | **27.5 mg ER (n=6)** | **52.5 mg ER (n=11)** | **77.5 mg ECER (n=10)** | **110 mg ECER (n=9)** |
| $C_{max}$ (ng/mL) | 63.2 (29.6) | 101 (88.4) | 139 (54.5) | 180 (76.6) |
| $t_{max}$ (h)[a] | 16.53 (3.02 – 168.00) | 12.00 (3.00 – 24.28) | 24.00 (5.93 – 71.25) | 24.00 (23.93 – 72.08) |
| $AUC_{0-168}$ (ng • h/mL) | 6130 (2840) | 9150 (10100) | 14600 (7530) | 18000 (9770) |
| $t_{1/2}$ (h) | 63.13 (24.67)[b] | 62.65 (34.74) | 73.66 (37.15)[c] | 53.47 (14.62) |
| $C_{168}$ (ng/mL) | 21.5 (19.3) | 24.7 (45.1) | 39.9 (32.3) | 42.0 (31.7) |

[a]Median (minimum-maximum).
[b]n=5.
[c]n=9.

Mean (SD) dehydro-aripiprazole PK variables after single-dose administration of the ER and ECER aripiprazole formulations to children and adolescents with TD in the fasted state are presented below:

| Mean (SD) Dehydro-aripiprazole PK Variables After Single-dose Administration of ER and ECER Formulations in the Fasted State | | | | | |
|---|---|---|---|---|---|
| **PK Variable** | **27.5 mg ER (n=6)** | **52.5 mg ER (n=6)** | **52.5 mg ECER (n=7)** | **77.5 mg ECER (n=6)** | **110 mg ECER (n=7)** |
| $C_{max}$ (ng/mL) | 9.26 (4.15) | 18.2 (8.49) | 13.8 (4.21) | 24.8 (10.9) | 30.0 (17.5) |
| $t_{max}$ (h)[a] | 71.94 (0.00[b] – 120.00) | 72.00 (71.83 – 168.02) | 24.00 (23.97 – 24.25) | 72.00 (71.28 – 167.75) | 73.72 (71.42 – 155.17) |
| $AUC_{0-168}$ (ng • h/mL) | 974 (490) | 2140 (905) | 1520 (373) | 3040 (1550) | 3450 (2010) |
| $t_{1/2}$ (h) | 78.33 (29.94)[b] | 152.50 (89.79)[b] | 78.34 (10.24)[b] | 136.56 (30.83)[c] | 168.82 (51.82)[c] |
| $C_{168h}$ (ng/mL) | 4.49 (3.20) | 13.8 (10.8) | 7.35 (1.50) | 19.2 (8.40) | 21.0 (11.4) |

[a]Median (minimum-maximum).
[b]n=4.
[c]n=3.

Mean (SD) dehydro-aripiprazole PK variables after administration of single-dose ER and ECER aripiprazole formulations to children and adolescents with TD in the fed state are presented below:

| Mean (SD) Dehydro-aripiprazole PK Variables After Single-dose Administration of ER and ECER Formulations With a High-fat Meal | | | | | |
|---|---|---|---|---|---|
| **PK Variable** | **27.5 mg ER (n=6)** | **52.5 mg ER (n=6)** | **52.5 mg ECER (n=7)** | **77.5 mg ECER (n=6)** | **110 mg ECER (n=7)** |
| $C_{max}$ (ng/mL) | 19.5 (16.8) | 9.15 (10.3) | 6.11 (5.12) | 8.91 (5.85) | 8.25 (5.01) |
| $AUC_{0-24}$ (ng • h/mL) | 226 (199) | 117 (143) | 47.6 (39.6) | 69.8 (55.2) | 70.1 (41.3) |

Note: The $C_{max}$ is based on 0-24 hours after dosing.

Mean (SD) dehydro-aripiprazole fed/fasted ratio PK variables after administration of single-dose ER and ECER aripiprazole formulations to children and adolescents with TD are presented below:

| Mean (SD) Fed/Fasted Ratio of Dehydro-aripiprazole PK Variables After Single-Dose Administration of ER and ECER Formulations With a High-fat Meal | | | | | |
|---|---|---|---|---|---|
| **PK Variable** | **27.5 mg ER (n=6)** | **52.5 mg ER (n=6)** | **52.5 mg ECER (n=7)** | **77.5 mg ECER (n=6)** | **110 mg ECER (n=7)** |
| Fed/Fasted Ratio $C_{max}$ | 3.51 (1.70) | 1.26 (1.19) | 1.39 (0.960) | 1.03 (0.938) | 1.35 (0.902) |
| Fed/Fasted Ratio $AUC_{0-24}$ | 3.94 (2.10) | 1.69 (1.39) | 1.08 (0.713) | 0.844 (0.897) | 1.37 (1.14) |

Note: The $C_{max}$ for fed/fasted ratios are based on 0-24 hours after dosing.

Mean (SD) dehydro-aripiprazole PK variables after multiple-dose weekly administration of the ER and ECER aripiprazole formulations are presented below:

| Mean (SD) Dehydro-aripiprazole PK Variables After Multiple-dose Weekly Administration of ER and ECER Formulations | | | | |
|---|---|---|---|---|
| **PK Variable** | **27.5 mg ER (n=6)** | **52.5 mg ER (n=11)** | **77.5 mg ECER (n=10)** | **110 mg ECER (n=9)** |
| $C_{max}$ (ng/mL) | 14.3 (7.04) | 20.9 (8.93) | 29.7 (14.4) | 47.0 (26.5) |
| $t_{max}$ (h)[a] | 72.00 (24.00 – 168.00) | 72.00 (23.98 - 96.00) | 71.98 (1.00 – 72.28) | 72.00 (0.00 – 73.00) |
| $AUC_{0-168}$ (ng • h/mL) | 1770 (697) | 2730 (1360) | 4070 (1930) | 6280 (3710) |
| $t_{1/2}$ (h) | 176.65 (169.25)[b] | 139.22 (121.32) | 217.04 (163.74)[c] | 143.84 (87.01)[d] |
| $C_{168}$ (ng/mL) | 9.99 (9.21) | 11.8 (9.06) | 19.6 (10.0) | 28.7 (18.6) |

[a] Median (minimum – maximum).
[b] n=5.
[c] n=9.
[d] n=8.

**Safety Results:**

- A total of 46 unique subjects were included in the safety analysis: 5 subjects participated in Phase A only, 13 subjects participated in Phase B only, and 28 subjects participated in both Phases A and B. All 46 subjects received at least one dose of trial drug.
- During Phase A, 21 subjects (63.6%) experienced 60 treatment-emergent adverse events (TEAEs), and the incidence of TEAEs generally increased with the dose of aripiprazole. Fewer subjects experienced TEAEs when dosed in the fed state (28.1%) compared with those dosed in the fasted state (60.6%). During Phase B, 26 subjects (63.4%) experienced 69 TEAEs; more de novo subjects (84.2%) experienced TEAEs than did rollover subjects (45.5%).

- The most common TEAEs overall during Phase A were nausea and headache (21.2% each). During Phase B, the most common TEAEs were somnolence (14.6%) and abdominal pain upper, fatigue, and nausea (12.2% each).
- During Phase A, all TEAEs were mild or moderate in intensity. During Phase B, two subjects experienced severe TEAEs: one subject in the 27.5 mg ER cohort experienced severe somnolence, which was considered by the Investigator to be probably drug-related, and one subject in the 110 mg ECER cohort experienced two events of severe alanine transaminase (ALT) increased, the first of which began before dosing on Day 1 and was considered by the Investigator to be not related to trial drug and the second of which occurred on Day 8 and was considered by the Investigator to be not likely related to trial drug.
- Overall, for subjects during Phase A, 15 subjects (45.5%) experienced TEAEs considered by the Investigator to be potentially drug-related. The most common potentially drug-related TEAEs were nausea (18.2%) and fatigue, headache, and vomiting (12.1% each). During Phase B, 13 subjects (31.7%) overall experienced TEAEs considered by the Investigator to be potentially drug-related. The most common potentially drug-related TEAEs were somnolence (12.2%) and fatigue and nausea (9.8% each).
- There were no deaths or SAEs reported during the trial. One de novo subject in the 110 mg ECER cohort discontinued from the trial during Phase B because of an AE (severe ALT increased), which began before dosing on Day 1, resolved with sequelae, recurred on Day 8, and was considered by the Investigator to be not likely related to trial drug.
- Overall, there were no clinically significant findings in other safety evaluations, including clinical laboratory test results, vital sign measurements, physical examination findings, and ECG results during the trial.
- There were no clinically significant increases in EPS as measured by the SAS, BARS, and AIMS during the trial.
- There were no reports of suicidal ideation or behavior or suicide attempts as measured by the C-SSRS during the trial.
- There were no results of concern on the CY-BOCS, PARS, CDRS-R, or CPRS-R:S during the trial

**Conclusions:**

- Overall, oral once-weekly ER and ECER tablet formulations of aripiprazole were safe and well-tolerated after single- and multiple-weekly doses in this pediatric population with TD.
- Aripiprazole $C_{max}$ and $AUC_{0-168}$ after single- and multiple-dose administration of once-weekly ER and ECER aripiprazole formulations increased with increasing doses of aripiprazole.
- Administration of ER and ECER formulations with food resulted in 1.60-3.57 times higher aripiprazole exposure based on $C_{max}$ and 1.18-1.93 times higher aripiprazole exposure based on $AUC_{0-24}$ based on aripiprazole concentrations during the 24 hours after its administration.

- The ECER formulation of aripiprazole administered once weekly exhibited less of a food effect compared with the ER formulation.
- Accumulation of the ECER formulation after multiple dosing was 1.02-1.46 times based on $C_{max}$ and $AUC_{0-168}$ PK variables.

Aripiprazole appears to show efficacy in this pediatric population with TD when assessed in an exploratory fashion by evaluating the change from baseline in YGTSS-TTS and CGI-S.

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**References:**

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