Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597)
Clinical Summary for Protocol 31-09-265

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

Indication:	Tourette's disorder
Clinical Development Phase:	1
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland, United States
Trial Initiation Date:	22 Mar 2010
Trial Completion Date:	21 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, Three Phase, Sequential Design, Single and Multiple Dose Study to Assess the Safety, Tolerability, and Pharmacokinetic Profile of an Enteric Coated Once-weekly Oral Formulation of Aripiprazole Administered to Children and Adolescents with Tourette's Disorder

Trial Center(s) by Region: Multicenter (13 centers; United States)

Clinical Phase/Trial Type: 1/Open-label, Multi-center, Non-comparative, 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 that is 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 D2 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 are under investigation are enteric coated (EC) and extended release (ER) oral tablets of aripiprazole. An EC capsule formulation was investigated in this trial. Although aripiprazole has been studied in children and adolescents, the pediatric subjects enrolled in this trial represent the first population to be administered the EC capsule formulation.

The age range for the subject population in this trial was 10 to 17 years, inclusive, for Phases A and B and 7 to 17 years, inclusive, for Phase C. These age ranges were 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 dose strengths of an EC aripiprazole capsule 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 an EC once-weekly oral formulation of aripiprazole after single and multiple weekly dose administration.
- PK: To determine the PK profile of aripiprazole and its metabolite, dehydro-aripiprazole, in plasma after single and multiple dose administration of a once-weekly EC formulation of aripiprazole in the fasted state and after single dose administration after a high-fat meal.

The secondary objective of this trial was to explore efficacy. The objective was to determine the potential efficacy based on the mean change from Baseline (Day 1 of each phase) in the Yale Global Tic Severity Scale (YGTSS) total score, Total Tic Score (TTS), and Clinical Global Impression - Severity of Illness Scale (CGI-S) score.

Methodology: This was an open-label, multicenter, three phase, sequential design, single and multiple dose trial to assess the safety, tolerability, and PK profile of an EC once-weekly oral capsule formulation of aripiprazole administered to children and adolescents with TD.

Phase A of the trial was to explore dose levels in a cross-over design and to assess the safety, tolerability, and PK profile of five dose strengths of an EC capsule formulation of aripiprazole (22.5, 37.5, 47.5, 60, and 75 mg). Originally, only the three lowest dose strengths were planned to be used in this trial: two subjects were to be enrolled into one of three cohorts and dosed sequentially with each of the three dose strengths in a protocol-specified order on Days 1, 8 and 15. The dosing order was as follows:

- Cohort 1 - 22.5-, 37.5-, and 47.5-mg EC capsules
- Cohort 2 - 37.5-, 47.5-, and 22.5-mg EC capsules
- Cohort 3 - 47.5-, 22.5-, and 37.5-mg EC capsules

The protocol was later amended to include the 60- and 75-mg dose strengths, with 6 subjects to be enrolled in a fourth cohort to receive both dose strengths in sequence. With this amendment, the original 3 cohorts were referred to as Phase A, Part 1 and the new fourth cohort was referred to as Phase A, Part 2. Dosing occurred on a weekly basis (ie, on Days 1, 8, and 15 for Part 1 and on Days 1 and 8 for Part 2). Initially, two subjects were dosed starting with the lowest strength of EC capsule (22.5 mg) in Phase

A. Safety, tolerability, and PK data were assessed at 48 hours and at Day 7 for the two subjects. The next dose (37.5 mg) was administered to these subjects only after the previous dose was deemed safe and tolerable (based on Day 7 safety and PK assessments). The same criteria were applied for the 47.5-mg dose. The next cohorts were dosed in their protocol-specified order after all doses were administered in Cohort 1 and deemed safe and tolerable. Subjects completing Phase A of the trial could have rolled over into Phase B and subsequently into Phase C. Alternatively, subjects completing Phase A could have continued directly into the dose level with ongoing enrollment in Phase C to avoid enrollment delays.

During Phase B of the trial, food effect was evaluated in 12 subjects (six at a low dose and six at a high dose determined during Phase A). Subjects entering Phase B from Phase A, Part 1, received the lowest dose EC capsule (ie, 22.5 mg), and subjects entering Phase B from Phase A, Part 2, received the highest tolerated dose (ie, 60 or 75 mg depending on the results of Phase A, Part 2). On Day 1 of Phase B, subjects received a single dose of either the low dose or high dose of EC capsule within 30 minutes after the start of a Food and Drug Administration-recommended high-fat meal. Safety and tolerability of the subjects were evaluated through Day 8. Subjects completing Phase B of the trial could have rolled over into Phase C.

During Phase C, the safety, tolerability, and the PK profile of multiple-dose administration were evaluated by assessing once-weekly administration of 22.5- or 37.5-mg EC capsules, or the highest-tolerated dose administered in Phase A, to 10 subjects each for 4 consecutive weeks. Dosing occurred on Days 1, 8, 15, and 22. For Phase C, the final safety and tolerability evaluation occurred on Day 29.

Number of Subjects: The expected number of subjects planned to be dosed during this trial was between 30 and 54 subjects. The planned number of subjects by trial phase was as follows: Phase A - 12 subjects (including Parts 1 and 2); Phase B - 12 subjects total (up to 12 subjects continuing from Phase A); and Phase C - 30 subjects total (up to 12 subjects continuing from Phase B).

A total of 61 unique subjects were screened for enrollment into the trial, and 36 unique subjects were enrolled and included in the safety and efficacy analyses: 9 subjects participated in Phases A, B, and C; 3 subjects participated in Phases A and C; 3 subjects participated in Phases B and C; 2 subjects participated in Phase A only; and 19 subjects participated in Phase C only.

Diagnosis and Main Criteria for Inclusion/Exclusion: Subjects must have been 10 to 17 years old, inclusive, for Phases A and B, and 7 to 17 years, inclusive, for Phase C of the trial. Subjects must have had a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - text revision (DSM-IV-TR) diagnosis of TD. Poor metabolizers of cytochrome P450 2D6 (CYP2D6) isoenzyme were excluded from

participation during Phases A and B of the trial, but were allowed to participate in Phase C.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Three EC dose strengths of an aripiprazole capsule formulation were used in this trial: EC capsule 22.5 mg, EC capsule 37. mg, and EC capsule 47.5 mg. Capsules were combined for doses of 60 mg (ie, 37.5- and 22.5-mg capsules) or 75 mg (ie, two 37.5-mg EC capsules).

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 all three phases of the trial, participation ranged from approximately 89 to 151 days (including 7 to 60 days for screening and washout, 15 to 22 days for Phase A, 8 days for Phase B, 29 days for Phase C, and 30 [+2] days for follow-up after the last dose of trial medication). The actual trial duration (first subject screened to last subject completed) was approximately 14 months.

Trial Assessments:

Efficacy: YGTSS and the CGI-S.

Safety: adverse events (AEs), clinical laboratory tests (serum chemistry, hematology, and urinalyses), vital signs, electrocardiograms (ECGs), extrapyramidal symptoms (EPS) assessments (Simpson Angus Scale [SAS], Barnes Akathisia Rating Scale [BARS], and Abnormal Involuntary Movement Scale [AIMS]), Columbia-Suicide Severity Scales (C-SSRS), physical examination, Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), Pediatric Anxiety Rating Scale (PARS), Children's Depression Rating Scale – Revised (CDRS-R), and the Conner's Parent Rating Scale – Revised: Short Version (CPRS-R:S).

PK: maximum (peak) plasma concentration (C_{max}), time to maximum (peak) plasma concentration (t_{max}), plasma concentration at 168 hours after dosing (C_{168h}), area under the concentration-time curve from time zero to 168 hours ($AUC_{0\text{-}168h}$) in Phases A and C, area under the concentration-time curve from time zero to 48 hours ($AUC_{0\text{-}48h}$) in Phases A and B, fed/fasted ratios of C_{max} and $AUC_{0\text{-}48h}$ (Day 8/Day 1) in Phase B to Phase A, elimination rate constant of the terminal elimination phase (λ_z) in Phases A and C only, and terminal-phase elimination half-life ($t_{1/2,z}$) in Phases A and C only.

Criteria for Evaluation:

Primary Outcome Variables:

- Safety: AEs, vital sign measurements (blood pressure, orthostatic reaction, and heart rate), height, weight, ECGs, clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, EPS, and clinical assessments, including evaluation of suicidality by using the C-SSRS scores. Other safety variables included the CY-BOCS, PARS, CDRS-R, and CPRS-R:S scores.
- PK: C_{max}, C_{168h}, AUC_{0-168h} for aripiprazole and dehydro-aripiprazole.

Secondary Outcome Variables:

- PK: t_{max} and $_{t1/2,z}$ for aripiprazole and dehydro-aripiprazole, and apparent clearance of aripiprazole from plasma after oral administration (CL/F).
- Efficacy analysis was exploratory. For Phase A of the trial, the within-subject difference among the assigned dose strengths (22.5, 37.5, 47.5, 60, and 75 mg) was calculated for Total YGTSS Score, TTS, and CGI-S. For Phase B of the trial, the mean change from Baseline (Day 1 of Phase B) to Day 8 in Total YGTSS Score, TTS, and CGI-S were calculated for the low-dose and high-dose EC capsules. For Phase C of the trial, the mean change from Baseline (Day 1 of Phase C) to Day 29 in Total YGTSS Score, TTS, and CGI-S were calculated for each dose examined in Phase C.

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).

PK: Plasma concentrations for aripiprazole and dehydro-aripiprazole were analyzed by noncompartmental methods. The following variables were determined: C_{max}, AUC_{0-24} and AUC_{0-168}, t_{max}, and $t_{1/2,z}$. Apparent clearance (CL/F) of aripiprazole from plasma after single oral administration (Dose/AUC_{∞} [area under the concentration- time curve from time 0 extrapolated to infinity]) was also calculated along with fed/fasted ratios of C_{max} and AUC_{0-24}. The in-vivo release profile for the EC capsule formulation after single-dose administration under fasting conditions was 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: Nine subjects participated in Phases A, B, and C; 3 subjects participated in Phases A and C; 3 subjects participated in Phases B and C; 2 subjects participated in Phase A only; and 19 subjects participated in Phase C only. During Phase A, 2 subjects (14.3%) in Cohort 4 discontinued because they met withdrawal criteria (urine drug screen results positive for cannabinoids at the Day 1 visit).

Of the 12 subjects (85.7%) who completed Phase A, 9 subjects (64.3%) rolled over into Phase B, 2 subjects (14.3%) rolled over into Phase C, and 1 subject (7.1%) rolled over into Phase C after a delay as a "de novo" subject. Three subjects were enrolled into Phase B without completing Phase A. All of the 12 subjects who participated in Phase B completed the phase and rolled over into Phase C. Nineteen subjects were enrolled into Phase C without completing Phase A or B. Of the 34 subjects who participated in Phase C, 6 subjects (17.6%) discontinued from the trial. Two subjects in the 22.5-mg EC dose group (1 de novo and 1 rollover subject) were discontinued because they met withdrawal criteria: one subject had a QTcB interval > 420 msec, and one subject was not able to complete the Day 22 visit on the scheduled date. Three de novo subjects in the 37.5-mg EC dose group were discontinued because of an AE: one subject had an AE of nausea, one subject had an AE of orthostatic hypotension, and one subject had an AE of worsening insomnia. One de novo subject in the 75-mg EC dose group was lost to follow-up after the Day 8 visit.

The majority of the 14 subjects who participated in Phase A were male (71.0%), white (71.0%), and not Hispanic or Latino (57.0%). Mean (SD) age was 13.14 years (2.25 years); age ranged from 10 to 17 years. Mean (SD) weight and BMI were 52.78 kg (14.89 kg) and 21.22 kg/m^2 (4.49 kg/m^2), respectively. For subjects participating in Phase B, most of the 12 subjects were male (83.0%), white (83.0%), and not Hispanic or Latino (58.0%). Mean (SD) age was 12.33 years (1.97 years); age ranged from 10 to 16 years. Mean (SD) weight and BMI were 51.88 kg (18.19 kg) and 21.67 kg/m^2 (5.68 kg/m^2), respectively. Of the 34 subjects participating in Phase C, the majority were male (74.0%), white (68.0%), and not Hispanic or Latino (68.0%). Mean (SD) age was 12.82 years (2.61 years); age ranged from 8 to 17 years. Mean (SD) weight and BMI were 58.09 kg (22.45 kg) and 22.94 kg/m^2 (6.05 kg/m^2), respectively.

Overall, the mean (SD) time since onset for TD for subjects in Phase A was 5.65 years (3.43 years), with a mean (SD) time since diagnosis of TD of 2.35 years (2.75 years). A total of 10 subjects also had concurrent ADHD and two subjects had concurrent OCD (CY-BOCS score ≤ 20); two subjects had concurrent ADHD and OCD. The mean (SD) TTS (ie, the sum of the total motor and vocal tic severity scores; maximum score of 50) was 32.21 (6.93). The mean (SD) YGTSS (ie, the sum of the TTS and the YGTSS ranking of impairment; maximum score of 100) was 63.64 (16.57).

For subjects enrolled in Phase B, the mean (SD) time since onset for TD and a mean (SD) time since diagnosis of TD of 5.82 years (3.37 years) and 3.36 years (3.29 years), respectively. A total of 10 subjects also had concurrent ADHD, and two subjects had concurrent OCD (CY-BOCS score ≤ 20); two subjects had concurrent ADHD and OCD. The mean (SD) TTS was 25.67 (7.48). The mean (SD) YGTSS was 49.83 (15.01).

For subjects enrolled in Phase C, the mean (SD) time since onset for TD was 5.47 years (3.62 years), with a mean (SD) time since diagnosis of TD of 2.98 years (3.27 years). A total of 20 subjects also had concurrent ADHD and four subjects had concurrent OCD (CY-BOCS score ≤ 20); three subjects had concurrent ADHD and OCD. The mean (SD) TTS was 26.65 (7.18). The mean (SD) YGTSS was 51.94 (13.55).

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 assessment 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 was greater at time points after Day 8 for Cohorts 1, 2, and 4. Cohort 3 had the greatest mean changes from baseline at all timepoints. When analyzed by using a linear mixed model, the estimated treatment effect increased with increasing dose when the 22.5-mg EC dose level was used as the reference group.
- Overall, during Phase B, mean change from baseline in YGTSS-TTS was similar between the two dose groups (ie, 22.5 and 75 mg). For both dose groups, the de novo subjects had a greater mean change from baseline compared with that of the rollover subjects; however, the small number of de novo subjects limits interpretation of this difference.
- During Phase C, all three dose groups (ie, 22.5, 37.5, and 75 mg) overall had mean decreases from baseline in YGTSS-TTS at almost all time points. Subjects in the 37.5- and 75-mg EC dose groups had greater mean decreases from baseline than did subjects in the 22.5-mg EC dose group, and de novo subjects generally had greater mean decreases from baseline than did rollover subjects.

- For subjects in Phase A, all cohorts had mean decreases from baseline in CGI-S at all timepoints, with Cohort 3 having the greatest mean decreases.
- During Phase B, mean decreases from baseline in CGI-S were seen in both dose groups and were similar overall.
- Mean decreases from baseline in CGI-S were seen at all timepoints overall and for de novo and rollover subjects during Phase C. Subjects in the 37.5- and 75-mg EC dose groups had somewhat greater mean decreases overall than did subjects in the 27.5-mg EC dose group.

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

Mean (SD) Aripiprazole PK Variables After Single-dose Administration of EC Aripiprazole Capsules in the Fasted State

PK Variable	22.5 mg EC (n=6)	37.5 mg EC (n=6)	47.5 mg EC (n=6)	60 mg EC (n=6)	75 mg EC (n=6)
C_{max} (ng/mL)	50.2 (4.60)	76.1 (14.7)	95.9 (20.6)	107 (47.3)	118 (24.3)
t_{max} (h)[a]	23.96 (8.93 – 24.08)	10.54 (6.00 – 24.07)	10.50 (8.97 – 24.02)	9.01 (6.00 – 72.03)	24.00 (6.00 – 72.00)
$AUC_{0\text{-}48h}$ (ng · h/mL)	1900 (164)	2900 (524)	3810 (701)	3790 (1490)	4350 (1360)
$AUC_{0\text{-}168h}$ (ng · h/mL)	4780 (1000)	6500 (707)	8350 (1400)	8430 (3050)	10200 (2110)
$t_{1/2}$ (h)	66.95 (40.27)	61.08 (35.04)	60.97 (34.12)	50.36 (15.96)	67.09 (62.96)
CL/F (L/h)	4.06 (1.35)	4.91 (1.04)	4.99 (1.40)	7.22 (3.51)	6.52 (2.76)
C_{168h} (ng/mL)	11.4 (7.85)	12.8 (7.54)	16.8 (11.6)	15.2 (9.09)	20.6 (16.7)

[a]Median (minimum-maximum).

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

Mean (SD) Aripiprazole PK Variables After Single-dose Administration of EC Aripiprazole Capsules With a High-fat Meal		
PK Variable	**22.5 mg EC (n=6)**	**75 mg EC (n=6)**
C_{max} (ng/mL)	83.4 (33.0)	212 (88.0)
t_{max} (h)[a]	12.02 (9.05 – 48.48)	9.04 (6.00 – 24.00)
AUC_{0-48h} (ng · h/mL)	3020 (1220)	7280 (3160)
C_{168h} (ng/mL)	13.0 (9.08)	22.1 (16.8)

[a] Median (minimum-maximum).

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

Mean (SD) Fed/Fasted Ratio of Aripiprazole PK Variables After Single-dose Administration of EC Aripiprazole Capsules		
PK Parameter	**22.5 mg EC (n=5)**	**75 mg EC (n=4)**
Fed/Fasted Ratio C_{max}	1.84 (0.474)	2.12 (1.31)
Fed/Fasted Ratio AUC_{0-48h}	1.72 (0.380)	1.85 (1.03)

Note: The Cmax for fed/fasted ratios are based on 0-48 hours after dosing.

Mean (SD) aripiprazole PK variables after multiple-dose weekly administration of EC aripiprazole capsules in the fasted state are presented below:

Mean (SD) Aripiprazole PK Variables After Multiple-dose Weekly Administration of EC Aripiprazole Capsules			
PK Variable	**22.5 mg EC (n=8)**	**37.5 mg EC (n=10)**	**75 mg EC (n=10)**
C_{max} (ng/mL)	75.1 (28.0)	153 (77.0)	196 (243)
t_{max} (h)[a]	9.04 (5.97 – 24.67)	6.00 (2.95 – 24.30)	6.00 (0.00 – 24.08)
AUC_{0-168h} (ng · h/mL)	5940 (2130)	12100 (6840)[b]	16900 (18700)
$t_{1/2}$ (h)	81.12 (65.11)	57.91 (27.75)[b]	73.42 (33.05)
C_{168h} (ng/mL)	14.2 (11.3)	24.7 (26.7)[b]	46.9 (74.8)

[a]Median (Minimum – Maximum).
[b]n=9.

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

Mean (SD) Dehydro-aripiprazole PK Variables After Single-dose Administration of EC Aripiprazole Capsules

PK Variable	22.5 mg EC (n=6)	37.5 mg EC (n=6)	47.5 mg EC (n=6)	60 mg EC (n=6)	75 mg EC (n=6)
C_{max} (ng/mL)	7.95 (1.37)	11.7 (3.38)	14.1 (4.22)	20.1 (11.6)	26.8 (8.51)
t_{max} (h)[a]	72.09 (71.93 – 119.33)	72.03 (71.52 – 166.80)	71.99 (71.47 – 119.40)	72.04 (24.00 – 120.63)	72.00 (71.67 – 168.00)
AUC_{0-48h} (ng·h/mL)	195 (48.3)	282 (107)	391 (161)	583 (425)	712 (348)
AUC_{0-168h} (ng · h/mL)	996 (164)	1430 (432)	1770 (613)	2400 (1290)	3180 (1090)
$t_{1/2}$ (h)	87.06 (9.18)[b]	106.51 (50.40)[c]	98.28 (26.87)[c]	117.08 (108.69)[c]	73.44 (13.88)[c]
C_{168h} (ng/mL)	5.42 (1.73)	7.06 (2.42)	8.65 (3.64)	9.02 (3.83)	13.5 (4.13)

[a]Median (minimum-maximum).
[b]n=2.

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

Mean (SD) Dehydro-aripiprazole PK Variables After Single-dose Administration of EC Aripiprazole Capsules With a High-fat Meal

PK Variable	22.5 mg EC (n=6)	75 mg EC (n=6)
C_{max} (ng/mL)	10.9 (3.06)	44.6 (28.1)
t_{max} (h)[a]	47.86 (47.43 – 48.48)	47.98 (24.00 – 48.17)
AUC_{0-48h} (ng · h/mL)	291 (96.7)	1330 (994)
C_{168h} (ng/mL)	6.25 (2.47)	19.3 (8.27)

[a]Median (minimum-maximum).
Note: The Cmax is based on 0-48 hours after dosing.

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

Mean (SD) Fed/Fasted Ratio of Dehydro-aripiprazole PK Variables After Single-dose Administration of EC Aripiprazole Capsules		
PK Variable	**22.5 mg EC (n=5)**	**75 mg EC (n=4)**
Fed/Fasted Ratio C_{max}	2.62 (0.740)	3.03 (1.62)
Fed/Fasted Ratio AUC_{0-48h}	1.67 (0.476)	1.92 (0.865)

Note: The Cmax for fed/fasted ratios are based on 0-48 hours after dosing.

Mean (SD) dehydro-aripiprazole PK variables after multiple-dose weekly administration of EC aripiprazole capsules in the fasted state are presented below:

Mean (SD) Dehydro-aripiprazole PK Variables After Multiple-dose Weekly Administration of EC Aripiprazole Capsules			
PK Parameter	**22.5 mg EC (n=8)**	**37.5 mg EC (n=10)**	**75 mg EC (n=10)**
C_{max} (ng/mL)	13.1 (4.69)	28.6 (9.64)	35.6 (21.1)
t_{max} (h)[a]	72.11 (24.00 – 168.00)	47.85 (23.95 – 72.00)	71.74 (3.00 – 120.83)
AUC_{0-168h} (ng · h/mL)	1680 (641)	4020 (1200)[c]	5060 (3340)
$t_{1/2}$ (h)	111.94 (55.04)[b]	105.03 (53.79)[d]	155.90 (99.31)[b]
C_{168h} (ng/mL)	6.95 (3.31)	15.8 (7.32)[c]	23.6 (18.4)

[a]Median (Minimum – Maximum).
[b]n=7.
[c]n=9.
[d]n=8.

Safety Results:

- A total of 36 unique subjects were included in the safety analysis: 9 subjects participated in Phases A, B, and C; 3 subjects participated in Phases A and C; 3 subjects participated in Phases B and C; 2 subjects participated in Phase A only; and 19 subjects participated in Phase C only. All 36 subjects received at least one dose of trial drug.
- During Phase A, 12 subjects (37.5%; 12 of 32 subjects as dosed in the cross-over design) experienced 43 treatment-emergent adverse events (TEAEs), and the incidence of TEAEs was similar for most doses of aripiprazole. During Phase B, eight subjects (66.7%) experienced 23 TEAEs. The incidence of TEAEs was the

same in both dose groups, but the subjects in the 75-mg EC dose group reported twice as many TEAEs as did subjects in the 22.5-mg EC dose group. During Phase C, 26 subjects (76.5%) experienced 73 TEAEs. The incidence of TEAEs was higher for subjects in the 37.5-mg EC dose group (92.3%) compared with the 22.5- and 75-mg EC dose groups (70.0% and 63.6%, respectively).

- The most common TEAEs overall during Phase A were nausea (35.7%), vomiting (28.6%), and sedation and somnolence (21.4% each). During Phase B, nausea and vomiting (33.3% each) were the most common TEAEs. The most common TEAEs during Phase C were nausea and vomiting (23.5% each) and dizziness (20.6%).
- During Phases A and B, all TEAEs were mild or moderate in intensity. During Phase C, four subjects experienced severe TEAEs: one subject in the 22.5-mg EC dose group experienced severe tooth abscess, one subject in the 37.5-mg EC dose group experienced severe affective disorder, one subject in the 37.5-mg EC dose group experienced severe insomnia, and one subject in the 75-mg EC dose group experienced severe sedation. Of these severe events, only the event of sedation was considered by the investigator to be potentially related to trial drug.
- Overall, for subjects during Phase A, 10 subjects (31.3%; 10 of 32 subjects as dosed in the cross-over design) experienced TEAEs considered by the investigator to be potentially drug-related. The most common potentially drug-related TEAEs were nausea, sedation, somnolence, and vomiting (9.4% each). During Phase B, seven subjects (58.3%) experienced TEAEs considered by the investigator to be potentially drug-related. The most common potentially drug-related TEAEs were nausea and vomiting (33.3% each) and sedation and somnolence (16.7% each). For subjects during Phase C, 15 subjects (44.1%) experienced TEAEs considered by the investigator to be potentially drug-related. The most common potentially drug-related TEAEs were nausea (23.5%), vomiting and dizziness (20.6% each), and somnolence (17.6%).
- There were no deaths reported during the trial. One SAE was reported during Phase C: one subject in the 37.5-mg EC dose group experienced a severe TEAE of affective disorder, which was also reported as an SAE and was considered by the investigator to be unrelated to trial drug. Three subjects in the 37.5-mg EC dose group discontinued from the trial during Phase C because of AEs (nausea, orthostatic hypotension, and insomnia). The events of nausea and orthostatic hypotension were considered to be potentially related to trial drug by the investigator.
- 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, the oral once-weekly EC capsule formulation of aripiprazole was safe and well-tolerated after single- and multiple-weekly administration of the doses evaluated in this trial in this pediatric population with TD.
- Aripiprazole Cmax and $AUC_{0\text{-}168h}$ after single- and multiple-dose administration of once-weekly EC aripiprazole capsule formulations increased with increasing doses of aripiprazole.
- Administration of EC capsule formulations with food resulted in 1.84 to 2.12 times higher aripiprazole exposure based on C_{max} and 1.72 to 1.85 times higher aripiprazole exposure based on $AUC_{0\text{-}48h}$ based on aripiprazole concentrations during the 48 hours after its administration.
- 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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