Official Title:	**A Randomized, Placebo-controlled Trial to Evaluate the Long-term (ie, Maintenance) Efficacy of Oral Aripiprazole in the Treatment of Pediatric Subjects with Tourette's Disorder**
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Protocol 31-14-204

Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Aripiprazole (OPC-14597)

REVISED CLINICAL PROTOCOL

A Randomized, Placebo-controlled Trial to Evaluate the Long-term (ie, Maintenance) Efficacy of Oral Aripiprazole in the Treatment of Pediatric Subjects with Tourette's Disorder

Protocol No. 31-14-204
IND No. 116003/EudraCT No. 2018-002270-48

CONFIDENTIAL - PROPRIETARY INFORMATION

Clinical Development Phase:	3b/4
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850 United States
Immediately Reportable Event	PRA Safety Fax Line North/South America: [redacted] or [redacted] EAPA (Europe, Asia-Pacific and Africa): [redacted] PRA Drug Safety Center Email Address North/South America: [redacted] EAPA (Europe, Asia-Pacific and Africa): [redacted]
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Protocol 31-14-204

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Abilify, Aripiprazole (OPC-14597)	Protocol No.: 31-14-204 IND No.: 116003 EudraCT No.: 2018-002270-48
Protocol Title:	A Randomized, Placebo-controlled Trial to Evaluate the Longer-term (ie, Maintenance) Efficacy of Oral Aripiprazole in the Treatment of Pediatric Subjects with Tourette's Disorder
Clinical Phase/Trial Type:	Phase 3b/4, Therapeutic use
Treatment Indication:	Tics associated with Tourette's disorder (TD) in children and adolescents
Objective(s):	Primary: The primary objective of the trial is to evaluate the long-term efficacy of aripiprazole once-daily treatment with oral tablets in pediatric subjects with TD. Secondary: The secondary objective of the trial is to evaluate the safety and tolerability of aripiprazole once-daily treatment with oral tablets in pediatric subjects with a diagnosis of TD.
Trial Design:	This Phase 3b/4 trial is a randomized, double-blind, placebo-controlled trial. The trial consists of 3 distinct phases: a pretreatment phase, open-label stabilization phase, and a double-blind randomized withdrawal phase. The trial will be conducted on an outpatient basis. Screening assessments may occur during 1 or more visits (as needed), and must occur in the clinic. The baseline visit will occur in the clinic, as well as the open-label stabilization phase visits on Weeks 1, 2, 4, 8, 12, 14,16, 18, and 20 and the double-blind, randomized withdrawal phase visits at Weeks 1, 2, 4, 8, and 12. All other visits will occur via telephone with direct patient visualization (except for open-label Week 3 which does not require direct patient visualization), web, in-clinic, or other acceptable means of contact. The pretreatment phase consists of the screening period and a washout period (when applicable). This period ensures the subject meets the inclusion/exclusion criteria, that the appropriate washout periods of their current treatments are completed, and establishes a baseline for the efficacy and safety measures.

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	The open-label stabilization phase will start with the baseline visit (Day 1). Doses will be titrated (based on 2 weight groups [< 50 kg or ≥ 50 kg]) during this phase to establish an optimal, stabilized aripiprazole dose for each subject. Dose adjustments are not permitted after the Week 8 visit. Starting at Week 2, subjects meeting the stabilization criteria (≥ 35% improvement [decrease] of Yale Global Tic Severity Scale [YGTSS] Total Tic Score [TTS]) who demonstrate a continued response as described (≥ 35% improvement [decrease] of YGTSS TTS) for 12 consecutive weeks, inclusive, with no more than one excursion of response criteria will enter the double-blind randomized withdrawal phase. Stabilization can be achieved by Week 14 at the earliest. Excursions will not be permitted at the end of the 12th consecutive week of stabilization (ie, the randomization visit). Subjects entering the double-blind randomized withdrawal phase will be randomized 1:1:1 to the half-dose aripiprazole arm, full-dose aripiprazole arm, or placebo arm. Randomization will be stratified by region and weight group. Doses in the aripiprazole arms will be based on each subject's stabilized dose from the open-label stabilization phase. Subjects will be monitored for relapse during the double-blind randomized withdrawal phase. Relapse is defined as a loss of ≥ 50% of the improvement experienced during the open-label stabilization phase (ie, improvement at the last assessment of YGTSS before randomization) on the YGTSS TTS. There will also be a safety follow-up period (30 + 3 days) after the last dose of investigational medicinal product (IMP) or after the clinical site is notified that the subject prematurely discontinued their IMP.
Subject Population:	The trial population will include pediatric subjects, 6 to 17 years of age, meeting the current Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) diagnostic criteria for TD. It is anticipated that approximately 228 subjects will be enrolled in the open-label stabilization phase in order to randomize approximately 114 subjects into the double-blind randomized withdrawal phase.
Inclusion/Exclusion Criteria:	Key Inclusion Criteria: 1) The subject is a male or female child or adolescent, 6 to 17 years of age (inclusive) at the time of signing the informed consent/assent. 2) The subject meets current DSM-5 diagnostic criteria for TD, documented at screening and made by an

adequately trained clinician, as confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version.

3) The subject has a TTS ≥ 20 on the YGTSS at screening and baseline (Day 1).
4) The subject, a caregiver, and the investigator must all agree that the presenting tic symptoms cause impairment in the subject's normal routines, which include academic achievement, occupational functioning, social activities, and/or relationships.
5) Females of childbearing potential (all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started) must have a negative pregnancy test and must not be pregnant or lactating.
6) Written informed consent must be obtained from the subject or a legally acceptable representative (eg, guardian or caregiver), in accordance with requirements of the trial site's institutional review board (IRB)/independent ethics committee (IEC) and local regulatory requirements, prior to the initiation of any protocol-required procedures. In addition, the subject, as required by the trial center's IRB/IEC, must provide informed assent at screening and as such must be able to understand that he or she can withdraw from the trial at any time.
7) Ability, in the opinion of the principal investigator, of the subject and the subject's legally acceptable representative (eg, guardian) or caregiver(s) to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, and discontinuation of prohibited concomitant medications, to read and understand the written word in order to complete subject-reported outcomes measures, and to be reliably rated on assessment scales.

Key Exclusion Criteria:

1) The subject presents with a clinical presentation and/or history that is consistent with another neurologic condition that may have accompanying abnormal movements.
   These include, but are not limited to, the following:

- Transient tic disorder
- Huntington's disease
- Parkinson's disease
- Sydenham's chorea
- Wilson's disease
- Mental retardation
- Pervasive developmental disorder
- Tardive dyskinesia
- Traumatic brain injury
- Stroke
- Restless legs syndrome

2) The subject has a history of schizophrenia, bipolar disorder, or other psychotic disorder.
3) Subjects who receive psychostimulants for the treatment of attention-deficit hyperactivity disorder (ADHD) and who have developed and/or had exacerbations of the tic disorder after the initiation of stimulant treatment. (Note that subjects with ADHD who are treated with psychostimulants and have not developed new tics or a worsening of their current tics can be included if all other enrollment obligations are met).
4) The subject currently has a primary diagnosis that meets DSM-5 criteria for mood disorder.
5) The subject has severe obsessive-compulsive disease, as evidenced by a Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score > 16.
6) The subject has taken aripiprazole within 1 month (30 days) of the screening visit.
7) The subject has a history of neuroleptic malignant syndrome.
8) Subject is a sexually active male or female of childbearing potential (FOCBP) (all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started) who will not agree to practice 2 acceptable methods of birth control or who will not remain abstinent during the trial and for 30 or 90 days following the last dose of IMP for females and males, respectively. Abstinence will be permitted if it is confirmed and documented at every trial visit.

9) The subject represents a significant risk of committing suicide based on history (suicide attempt in past 1 year), routine psychiatric status examination, investigator's judgment, or who has an answer of "yes" on any question other than 1-3 (current or over the last 30 days) on the baseline/screening version of the Columbia-Suicide Severity Rating Scale (C-SSRS).
10) The subject has a body weight < 16 kg.
11) Subjects who have taken neuroleptic or antiparkinson drugs within 14 days prior to baseline.
12) Subjects requiring cognitive-behavioral therapy (CBT) for TD during the trial period. CBT for other nonexclusionary disorders must remain consistent throughout the trial.
13) The subject has met DSM-5 criteria for any significant psychoactive substance use disorder within the past 3 months.
14) A positive drug screen for cocaine, alcohol, or other drugs of abuse (excluding caffeine, nicotine, or prescribed psychostimulants for ADHD). Investigators can choose to repeat a positive drug screen one time during screening period after concurrence from the medical monitor. A second positive test for any drug of abuse would be exclusionary.
15) Subject requiring medication not allowed per protocol.
16) Use of any cytochrome P450 (CYP)2D6 and CYP3A4 inhibitors or CYP3A4 inducers within 14 days prior to baseline and for the duration of the trial.
17) Other nutritional or dietary supplements and nonprescription herbal preparations for TD (eg, cannabinoids, N-aceytlcysteine, omega-3 fatty acids, kava extracts, GABA supplements) within 7 days prior to baseline and for the duration of the trial, unless approved in advance by the medical monitor.
18) The inability to swallow tablets or tolerate oral medication.
19) Subject has participated in a clinical trial involving either study medication or interventional (non-medication) treatment for TD within the last 60 days.
20) The following laboratory test results, vital signs and electrocardiogram (ECG) results are exclusionary:

	a) Platelets ≤ 75,000/mm^3 b) Hemoglobin ≤ 9 g/dL c) Neutrophils, absolute ≤ 1000/mm^3 d) Aspartate aminotransferase > 3 × upper limit of normal (ULN) as defined by the central laboratory e) Alanine aminotransferase > 3 × ULN as defined by the central laboratory f) Creatinine ≥ 2 mg/dL g) Diastolic blood pressure > 105 mmHg h) Corrected QT interval ≥ 450 msec (males) or ≥ 470 msec (females) using the corrected QT interval for heart rate using Fridericia's formula
Trial Site(s):	Approximately 70 sites worldwide will be used in this trial.
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Once-daily oral aripiprazole will be administered every day, without regard to meals. Four dose strengths of an aripiprazole immediate release tablet formulation will be used in this trial: 2.0 mg, 5.0 mg, 10.0 mg, and 15.0 mg. Matching placebo tablets will be used in the double-blind randomized withdrawal phase. The 20.0 mg/day dose taken as two 10.0 mg tablets During the open-label stabilization phase, all enrolled subjects will begin treatment at a 2.0 mg/day dose, with the dose titrated to 5.0 mg/day after 2 days. Subsequent dose adjustments in set increments will be based on the subject's weight to achieve optimum control of tics up to the maximum recommended doses based on the United States (US) labeling. Subjects will be allowed one down titration during the open-label stabilization phase. Dose adjustments, and a subsequent return to the highest dose, are not allowed after the Week 8 visit. During the double-blind randomized withdrawal phase, subjects meeting the stabilization criteria will be randomized in a 1:1:1 ratio to the half-dose aripiprazole arm, full-dose aripiprazole arm, or placebo arm based on their stabilized dose in the open-label stabilization phase. All subjects will take 2 tablets per day.
Trial Assessments:	Efficacy: YGTSS TTS, Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) Severity, CGI-TS Improvement.

	Safety: Adverse event (AE) reporting, clinical laboratory tests, 12-lead ECG, vital signs, and physical examination. In addition, the subject's height, body weight, body mass index (BMI), waist circumference, serum prolactin (blinded), glycosylated hemoglobin, and thyroid-stimulating hormone (TSH) will be monitored. The C-SSRS (children's version) will be used to assess the risk of suicide events during the trial at every visit. Extrapyramidal symptoms (EPS) will be assessed using the following scales: Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), and Barnes Akathisia Rating Scale (BARS). Screening/Other: Screening evaluations include psychiatric, medical and medication history, CY-BOCS, urine drug and blood alcohol screen(s), and urine pregnancy tests.
Criteria for Evaluation:	**Primary Endpoint:** The primary efficacy endpoint is the time from randomization to relapse during the double-blind randomized withdrawal phase. **Exploratory Efficacy Endpoint:** The other efficacy endpoints include the following: • Mean change from randomization to last visit (Week 12 for completers and withdrawal visit for discontinued subject) in YGTSS TTS score • Mean change from randomization to last visit (Week 12 for completers and withdrawal visit for discontinued subject) in Total YGTSS score • Mean change from randomization to last visit (Week 12 for completers and withdrawal visit for discontinued subject) in CGI-TS Severity score • CGI-TS Improvement score at last visit (Week 12 for completers and withdrawal visit for discontinued subject) **Safety Endpoints:** Safety endpoints include the following: • AEs • Laboratory tests (hematology, serum chemistry [including prolactin (blinded), glycosylated hemoglobin, and TSH], urinalysis, and urine pregnancy tests) • Vital signs • ECGs

	• AIMS • BARS • SAS • C-SSRS • Body weight • BMI • Waist circumference
Statistical Methods:	The planned sample size for the randomization phase is 114 subjects (ie, 38 subjects per treatment group). Assuming the proportion of randomized subjects experiencing relapse during the double-blind randomized withdrawal phase will be 65% in the placebo group and 34% in each of the 2 aripiprazole dose groups, 114 subjects will provide approximately 80% power to detect a hazard ratio of 0.4 for relapse (either aripiprazole dose group versus placebo) at the alpha level of 0.05 (2-sided). Under the above assumptions, a total of 51 relapse events are expected to be observed during the randomization phase. However, subject enrollment will stop when 51 relapse events have accrued or 114 subjects have been randomized, whichever occurs earlier. Sample size will allow one interim analysis (IA) at approximately 70% of events accrual time point. The O'Brian-Fleming boundaries were used for sample size calculation of the IA so that the IA will be conducted after 36 relapse events are observed. The two-sided alpha levels for the IA is 0.016, and the alpha left for the final analysis will be 0.045. In order to randomize 114 subjects, approximately 228 subjects need to enter the open-label stabilization phase assuming the stabilization rate is 50%. The primary endpoint is time from randomization to relapse during the double-blind randomized withdrawal phase. Subjects who complete or discontinue from the double-blind randomized withdrawal phase without relapses will be considered as censored observations. The hazard ratio and its 95% confidence interval (CI) will be estimated from the Cox proportional hazard model with treatment as a factor. The p- value from the log rank test will be presented to compare survival (subjects free of relapse) distributions, ie, Kaplan-Meier curves, between the treatment groups.

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Trial Duration:	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 3 years and 4 months including an estimated 30 month recruitment period. Individual participation for subjects who complete the trial can range from a minimum of approximately 30 weeks to a maximum of 42 weeks.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADHD	Attention-deficit hyperactivity disorder
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BUN	Blood urea nitrogen
CBT	Cognitive-behavioral therapy
CGI-TS	Clinical Global Impressions Scale for Tourette's Syndrome
CNS	Central nervous system
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
CYP	Cytochrome P450
D_2	Dopamine D_2
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
ET	Early termination
EOP	End of phase
EU	European Union
FDA	(United States) Food and Drug Administration
FOCBP	Female of childbearing potential
GCP	Good Clinical Practice
5-HT	Serotonin type receptor
IA	Interim analysis
IAF	Informed assent form
IARC	Interim analysis review committee
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board
IRE	Immediately reportable event
IRT	Interactive response technology
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version
LDH	Lactate dehydrogenase
MNAR	Missing not at random
OCD	Obsessive-compulsive disorder

OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PK	Pharmacokinetics
PQC	Product quality complaint
QTcF	Corrected QT interval for heart rate using Fridericia's formula
RBC	Red blood cell
SAE	Serious adverse event
SAS	Simpson-Angus Scale
SNRI	Selective norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
T_3	Triiodthyronine
T_4	Thyroxine
TD	Tourette's disorder
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
TTS	Total Tic Score
US	United States
ULN	Upper limit of normal
WBC	White blood cell
YGTSS	Yale Global Tic Severity Scale

1 Introduction

Abilify® (aripiprazole) is approved for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults in the United States (US), the European Union (EU), Canada, and several other countries, and as adjunctive treatment in adult patients with major depressive disorder in the US, Canada, and Japan. Abilify is also approved in the US, EU, and Canada as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder in adult patients, and these approved claims have been extrapolated to children and adolescents in the US. In addition, Abilify is approved for the treatment of schizophrenia in adolescents in the US (ages 13 - 17 years), Canada (ages 15 - 17 years), and EU (ages ≥ 15 years), for the treatment of bipolar I disorder in children and adolescents in the US (ages 10 - 17 years), and Canada (ages 13 -17 years), for the treatment of severe manic episodes in bipolar I disorder in the EU (ages ≥ 13 years), and for the treatment of irritability associated with autistic disorder in the US in children and adolescents 6 to17 years of age. Aripiprazole is currently approved for treatment of Tourette's disorder (TD) in children and adolescents (6 - 18 years) in the US, the Republic of Korea, Philippines, Thailand, Indonesia, Taiwan, and Egypt.

Tourette's disorder is a neuropsychiatric condition that is 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.[1] 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.[2,3] Although the precise etiology of TD remains unknown, disturbances in serotonergic and/or dopaminergic pathways have been implicated because of the close association between TD and other disorders that involve imbalances in serotonin and/or dopamine (eg, obsessive-compulsive disease and attention-deficit hyperactivity disorder [ADHD]).[4,5] 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. Previous TD trials demonstrated the efficacy of aripiprazole over an 8-week period. This trial is part of the post-marketing commitment to evaluate the longer-term efficacy of aripiprazole.

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1.1 Nonclinical Data

The mechanism of action of aripiprazole differs from that of most currently marketed typical and atypical neuroleptics. It has been proposed that aripiprazole's effectiveness in schizophrenia is mediated through a combination of partial agonism (agonism/antagonism) at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_2 receptors. Aripiprazole has the properties of an agonist in an animal model of dopaminergic hypoactivity and the properties of an antagonist in animal models of dopaminergic hyperactivity. Aripiprazole exhibits high affinity for dopamine D_2 and D_3 and serotonin 5-HT_{1A} and 5-HT_{2A} receptors, and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic, and histamine H_1 receptors, and the serotonin reuptake site. Aripiprazole also displays 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist activity in nonclinical studies.

Please refer to the Investigator's Brochure (IB) for more detailed information.[6]

1.2 Clinical Data

Information about relevant clinical studies in the pediatric population is presented below. Please refer to the IB for more detailed information.[6]

1.2.1 Trial 31-12-293

The primary purpose of this phase 3, multicenter, randomized, double-blind, placebo-controlled, outpatient trial was to compare the efficacy of aripiprazole with placebo in the treatment of tics in children and adolescents (ages 7 - 17 years) with a diagnosis of TD over 8 weeks of treatment. The secondary purpose was to evaluate the safety and tolerability of aripiprazole once-daily treatment (5 - 20 mg/day) with oral tablets.

Efficacy was demonstrated by the statistically significant results achieved for the primary (Yale Global Tic Severity Scale [YGTSS] Total Tic Score [TTS]) and key secondary (Clinical Global Impressions Scale for Tourette's Syndrome [CGI-TS] Change Score) endpoints, as well as other secondary endpoints of the total YGTSS score, Clinical Global Impressions Scale [CGI]-Severity Score, and response rate (for the high-dose aripiprazole group). The primary efficacy analysis demonstrated that both low and high doses of aripiprazole were superior to placebo in the treatment of tics based on the YGTSS TTS score ($p = 0.0020$ for low-dose and $p < 0.0001$ for high-dose aripiprazole after multiplicity adjustment). The key secondary efficacy analysis also showed that both low- and high-doses of aripiprazole were superior to placebo in CGI improvement

(p = 0.0002 for low-dose and p = 0.0002 for high-dose aripiprazole after multiplicity adjustment).

The results of this trial demonstrated that the efficacy of aripiprazole as a treatment of tics associated with TD was robust. The results also demonstrated that the onset of efficacy started as early as 1 week after the initiation of treatment. Further, the efficacy of aripiprazole was demonstrated across a variety of demographic subgroups (age, region, race, and baseline YGTSS TTS). Importantly, the results are consistent with and confirm the evidence of efficacy seen in other trials, most notably Trial 031-KOA-0703, a double-blind, placebo-controlled trial in children and adolescents conducted in Korea.[7] The results are also consistent with the findings from a number of open-label and case studies in children and adolescents with TD reported in the published literature.[7,8,9,10,11] In aggregate, more than 500 children between 6 and 18 years of age were treated with aripiprazole from 2 weeks to 24 months in these trials. The literature indicated a significant reduction in the frequency and severity of tics, as assessed by the YGTSS, following treatment with aripiprazole. Overall, the average reduction in the total tic score was 47.1%; this reduction is consistent with the findings in Trial 31-12-293. In addition, the aripiprazole safety data reported in these trials did not differ from the side-effect profile that has been previously reported.

1.2.2 Trial 31-12-294

The primary purpose of this phase 3, multicenter, open-label trial was to evaluate the long-term safety and tolerability of aripiprazole once-daily treatment with oral tablets in children and adolescents (7 - 17 years of age) with a diagnosis of TD. The secondary purpose was to evaluate the efficacy of once-daily aripiprazole in the suppression of tics in children and adolescents with a diagnosis of TD, as measured by change from baseline to Week 52 on the TTS of the YGTSS.

Subjects who successfully completed Trial 31-12-293 were eligible to enter this extension trial, provided that continuation of treatment was clinically warranted, as judged by the investigator, and there had been no significant protocol violations or clinically relevant AEs that would preclude their inclusion in the trial.

Aripiprazole was generally well tolerated in this trial. The safety and tolerability of aripiprazole, as demonstrated in this trial, was reflected in no subjects experiencing a fatal serious adverse event (SAE), 4 subjects experiencing nonfatal SAEs (none deemed related to investigational medicinal product [IMP]), and 10 subjects experiencing treatment-emergent adverse events (TEAEs) leading to IMP discontinuation (5 subjects

for the event of weight increased). In addition, 40.0% and 31.8% of subjects overall experienced mild and moderate TEAEs, respectively, with 4.5% of subjects experiencing severe TEAEs. Fifty-six subjects (50.9%) had TEAEs that the investigator considered potentially related to IMP, with the events of weight increased, somnolence, and fatigue accounting for 45 of these subjects.

The efficacy analyses demonstrated that once-daily aripiprazole, as shown in the parent Trial 31-12-293, is effective in the treatment of tics associated with TD in children and adolescents (aged 7 - 18 years). In addition, these analyses demonstrated that subjects not currently taking aripiprazole, versus subjects with prior exposure (ie, subjects who received aripiprazole in Trial 31-12-293), yielded greater improvement in TD symptoms as measured by YGTSS TTS, CGI-TS change and severity scores, and total YGTSS score.

In summary, the data from this 52-week extension trial of subjects who participated in the parent Trial 31-12-293 demonstrated a favorable safety and tolerability profile of aripiprazole once-daily treatment in children and adolescents and its efficacy in the suppression of tics in this population.

1.3 Known and Potential Risks and Benefits

As of 01 Jun 2017, approximately 2300 children and adolescents with schizophrenia, bipolar disorder, autistic disorder, conduct disorder, or TD have been treated with once-daily or once-weekly oral aripiprazole in clinical trials.[6]

Commonly observed adverse reactions associated with the use of aripiprazole in pediatric patients with TD (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite.[12]

Additional safety and prescribing information can be found in the product label, which is attached to the IB.[6]

2 Trial Rationale and Objectives

2.1 Trial Rationale

The goal of this trial is to evaluate the longer-term efficacy of aripiprazole in pediatric subjects (6 - 17 years) for the treatment of TD. The trial has a pretreatment phase, up to a 20-week open-label stabilization phase, a 12-week double-blind randomized withdrawal

phase, and a 1 month follow-up period after the last dose of IMP or after the clinical site is notified that the subject discontinued the IMP. The proposed age range for the population in this trial is 6 to 17 years, inclusive. These age ranges are based on published data indicating that tics associated with TD show the greatest severity at 10 years of age. Previous TD trials demonstrated the efficacy of aripiprazole over an 8-week period. This trial is part of the US Food and Drug Administration (FDA) post-marketing commitment to evaluate the longer-term efficacy of aripiprazole.

2.2 Dosing Rationale

Based on the approved labeling aripiprazole in the US for TD, the 5 to 20 mg once-daily tablets are expected to result in safe, tolerable, and efficacious aripiprazole concentrations.[12] The goal of this trial is obtain long-term efficacy, safety, and tolerability data in a controlled condition of a once-daily aripiprazole formulation in children and adolescents with TD. Additionally, this trial will evaluate if the long-term therapeutic benefit is maintained with a lower dose of aripiprazole.

2.3 Trial Objectives

2.3.1 Primary

The primary objective of the trial is to evaluate the long-term efficacy of aripiprazole once-daily treatment with oral tablets in pediatric subjects with TD.

2.3.2 Secondary

The secondary objective of the trial is to evaluate the safety and tolerability of aripiprazole once-daily treatment with oral tablets in pediatric subjects with a diagnosis of TD.

3 Trial Design

3.1 Type/Design of Trial

This phase 3b/4 trial is a randomized, double-blind, placebo-controlled trial to evaluate the long-term efficacy of oral aripiprazole in the treatment of pediatric subjects with TD. Subjects will be recruited at approximately 70 sites globally. The trial consists of 3 distinct phases: a pretreatment phase, an open-label stabilization phase, and a double-blind randomized withdrawal phase. Screening assessments may occur during 1 or more visits (as needed), and must occur in the clinic. The baseline visit will occur in the clinic, as well the open-label stabilization phase visits on Weeks 1, 2, 4, 8, 12, 14, 16,

18, and 20 and the double-blind, randomized withdrawal phase visits at Weeks 1, 2, 4, 8, and 12. All other visits will occur via telephone with direct patient visualization (except for open-label Week 3 which does not require direct patient visualization), web, in-clinic, or other acceptable means of contact.

The pretreatment phase consists of the screening period and a washout period (when applicable). This period ensures the subject meets the inclusion/exclusion criteria, that the appropriate washout periods are completed, and establishes a baseline for efficacy and safety measures.

The open-label stabilization phase will start with the baseline visit (Day 1). Doses will be titrated (based on 2 weight groups [< 50 kg or ≥ 50 kg]) during this phase to establish an optimal, stabilized aripiprazole dose for each subject. Dose adjustments are not permitted after the Week 8 visit. Starting at Week 2, subjects meeting the stabilization criteria (≥ 35% improvement [decrease] of YGTSS TTS) who demonstrate a continued response as described (≥ 35% improvement [decrease] of YGTSS TTS) for 12 consecutive weeks, inclusive; with no more than one excursion of response criteria will enter the double-blind randomized withdrawal phase. Excursions are defined by loss of stabilization (< 35%) in YGTSS TTS. If a subject misses a visit, it will be considered an excursion, but if they miss a dose, it will not be considered an excursion. Stabilization can be achieved by Week 14 at the earliest. Excursions will not be permitted at the end of the 12th consecutive week of stabilization (ie, the randomization visit).

Subjects entering the double-blind randomized withdrawal phase will be randomized 1:1:1 to the half-dose arm, full-dose arm, or placebo arm. Doses in the aripiprazole arms will be based on the subject's stabilized dose during the single-blind stabilization phase. Subjects will be monitored for relapse during the double-blind randomized withdrawal phase. Relapse is defined as a loss of ≥ 50% of the improvement experienced during the open-label stabilization phase (ie, improvement at the last assessment of YGTSS before randomization) on the YGTSS TTS. If a subject meets relapse criteria, they should be discontinued and treated according to the schedule of assessments.

There will also be a safety follow-up period (30 + 3 days) after the last dose of IMP or after the clinical site is notified that the subject prematurely discontinued their IMP.

During the pretreatment phase, modifications to a subject's pre-existing treatment are not to be made for the explicit purpose of entering this trial, but should be done only where deemed clinically appropriate by the investigator. Tapering rates for washout of medications are at the discretion of the investigator and are to be determined on an

individual basis, with consideration to the subject's clinical condition, dose, and known pharmacokinetics (PK) of the medication being tapered, as long as the protocol-mandated discontinuation timeframe is met. The exception is a long-acting depot medication, which cannot be tapered and would be discontinued after the informed consent/assent is obtained.

All psychotropic medications and any medications used to treat tics must be discontinued for at least 2 weeks (14 days) prior to the baseline visit, with the exception of psychostimulant medications such as, but not limited to, Vyvanse, Adderall, Concerta, Metadate CR, Ritalin LA, Focalin, and Focalin XR, prescribed for the treatment of symptoms of ADHD, which are permitted during the trial. Use of psychostimulant medications is only permitted if the subject does not develop and/or have an exacerbation of the tic disorder after the initiation of treatment with the psychostimulant. In addition, the dose of any psychostimulant must have been stable for at least 4 weeks prior to screening. All selective serotonin reuptake inhibitors (SSRIs)/selective norepinephrine reuptake inhibitors (SNRIs) must be discontinued at least 4 weeks (28 days) prior to the baseline visit. In addition, once-weekly formulation of neuroleptics must be discontinued at least 4 weeks (28 days) prior to the baseline visit; long-acting (depot) neuroleptics must be discontinued for at least 1 full cycle (2 weeks to 1 month, depending on the drug) plus 2 weeks prior to the baseline visit. Clonidine, guanfacine, guanabenz, atomoxetine and carbamazepine are prohibited during the trial and must be discontinued for at least 2 weeks prior to baseline. Subjects must have discontinued aripiprazole treatment at least 30 days prior to the screening visit. Subjects not in need of medication washout may proceed to the trial baseline visit after the inclusion/exclusion criteria have been met.

During the open-label stabilization phase, visits will occur at Week 1 (± 2 days) for the titration visit and at Weeks 2, 3, and 4 (± 2 days) and Weeks 6, 8, 10, 12, 14, 16, 18, and 20 (± 3 days) for the stabilization visits, at which time efficacy and safety measures will be collected. Starting at Week 2, subjects meeting the stabilization criterion (≥ 35% improvement [decrease] of YGTSS TTS) who demonstrate a continued response as described (≥ 35% improvement [decrease] of YGTSS TTS) for 12 consecutive weeks, inclusive, with no more than one excursion of response criteria will enter the double-blind randomized withdrawal phase. Excursions will not be permitted at the end of the 12th consecutive week of stabilization (ie, the randomization visit). At Week 8, subjects will be discontinued if they no longer have the opportunity to achieve 12 weeks of response in the open-label stabilization phase (eg, the subject has not achieved a response).

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Upon entering the double-blind randomized withdrawal phase, subjects will be randomized to aripiprazole full dose, aripiprazole half dose, or placebo. Subjects will have trial visits at Weeks 1, 2, 3, and 4 (± 2 days) and Weeks 6, 8, 10, and 12 (± 3 days), at which time efficacy and safety measures will be collected. Subjects will be followed up for safety for 30 days after the last dose of IMP or after the clinical site is notified that the subject discontinued the IMP. The trial schematic is presented in Figure 3.1-1.

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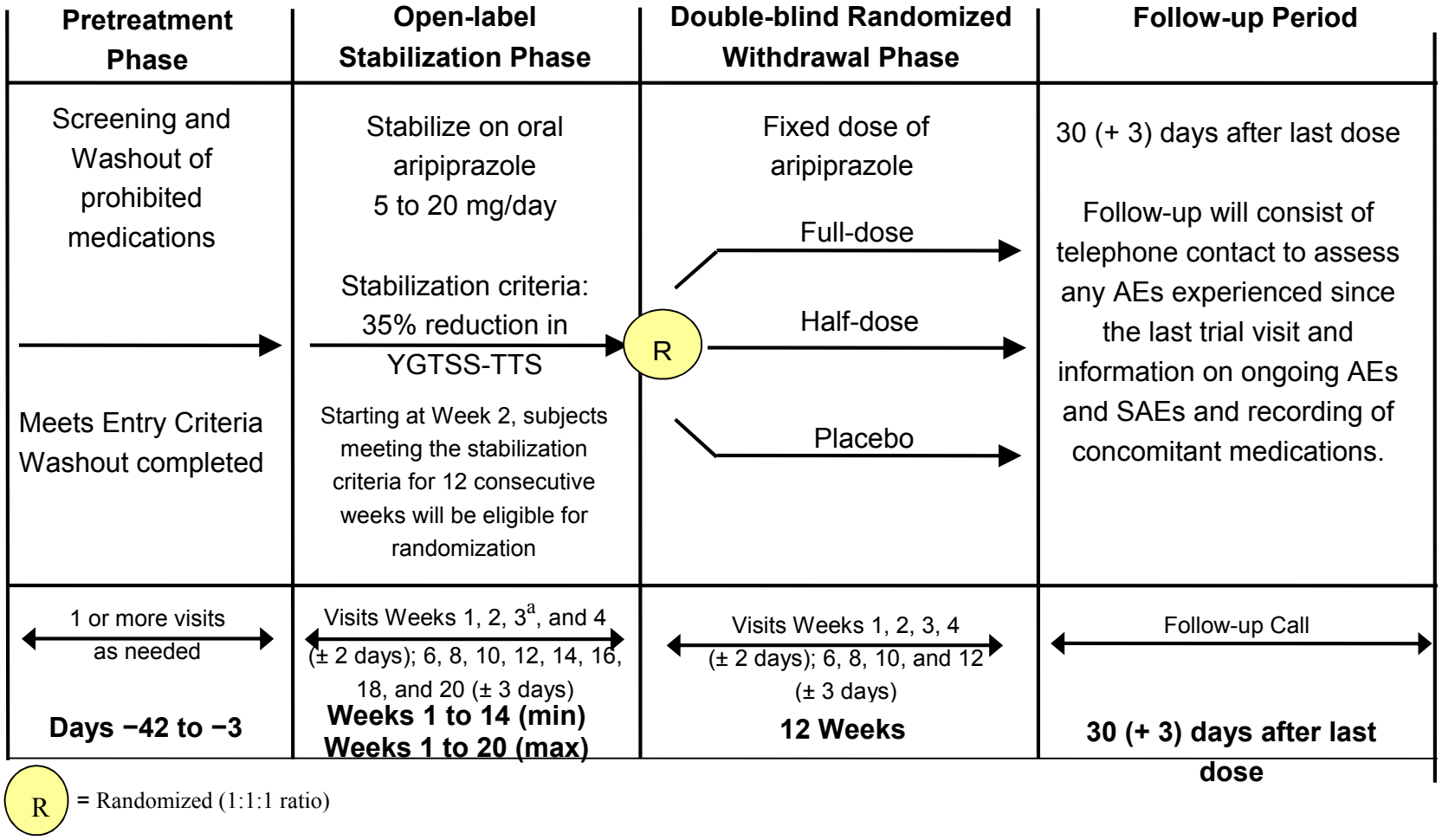

Figure 3.1-1 Trial Design Schematic

[a]Week 3 Visit will consist of a phone call to assess safety and tolerability. If dose adjustments are required, the subject will have an in-clinic visit for IMP dispensing.

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3.2 Trial Treatments

Four dose strengths of an aripiprazole immediate release tablet formulation will be used in this trial: 2.0 mg, 5.0 mg, 10.0 mg, 15.0 mg. Matching placebo tablets will be used in the double-blind randomized withdrawal phase.

Once-daily oral aripiprazole will be administered at approximately the same time every day beginning at baseline. Doses may be taken without regard to meals.

3.2.1 Open-label Stabilization Phase

All enrolled subjects will begin treatment at a 2.0 mg/day dose, with the dose titrated to 5.0 mg/day after 2 days. Subsequent dose adjustments in set increments will be based on the subject's weight at baseline to achieve optimum control of tics up to the maximum recommended doses based on the US labeling, presented in Table 3.2.1-1.

Table 3.2.1-1 US Labeling Information

Weight Group	Dosing Adjustments	Target Doses for Stabilization	Maximum Dose
< 50 kg	5 mg and 10 mg	5 mg and 10 mg	10 mg/day
≥ 50 kg	5 mg, 10 mg, and 20 mg	10 mg and 20 mg	20 mg/day

The dose titration schedule per weight group is provided in Table 3.2.1-2. Subjects with body weight < 50 kg must remain on a minimum stable dose of 5.0 mg or maximum 10.0 mg for a minimum of 12 weeks. Subjects with body weight ≥ 50 kg must achieve a dose of 10.0 mg no later than Week 4 and remain on a stable dose of 10.0 mg or 20.0 mg for a minimum of 12 weeks. For the remainder of the 12 week period, subjects can remain of 10.0 mg or titrate to 20.0 mg as long as efficacy is stable. In order to be titrated from 10.0 mg to 20.0 mg, subject must remain on a dose of 15.0 mg for 1 week (ie, at least 4 days) prior to being titrated to 20.0 mg. If a subject is titrated to 20.0 mg and subsequently requires down-titration, their dose will be reduced to 10.0 mg. If the dose is up-titrated again, the dose must increase from 10.0 mg to 20.0 mg without a 15.0 mg step.

Subjects will be allowed one down titration (only to the minimum dose to achieve stabilization) and a return to the prior maximum dose during the open-label stabilization phase. Up-titration can only occur at scheduled visits, but down-titration may occur at either scheduled or unscheduled visits. Dose adjustments, and a subsequent return to the higher dose, are not allowed after the Week 8 visit. If a subject experiences an AE or tolerability issues after the Week 8 visit that require the dose to be down-titrated,

regardless of dose level, they must be discontinued. Subjects who meet the YGTSS TTS criteria for stability and remain on a stable dose of IMP for 12 weeks may be randomized into the double-blind phase of the trial prior to the Week 20/EOP visit.

Table 3.2.1-2 Open-label Stabilization Phase Dosing Schedule

Body Weight	Day 1 (Baseline)	Week 1	Week 2	Week 4	Week 8[a]	Weeks 12 to 20[a]
< 50 kg	2.0 mg starting dose, increased to 5.0 mg after 2 days	5.0 mg or increase to 10.0 mg	5.0 mg or increase to 10.0 mg	5.0 mg or increase to 10.0 mg	5.0 mg or increase to 10.0 mg	5.0 mg or 10.0 mg
≥ 50 kg	2.0 mg starting dose, increased to 5.0 mg after 2 days	5.0 mg or increase to 10.0 mg	5.0 mg or increase to 10.0 mg or 20.0 mg (via 15.0 mg step)[b]	10.0 mg or increase to 20.0 mg[b]	10.0 mg or 20.0 mg[b]	10.0 mg or 20.0 mg

[a]A one-time down-titration and a return to the previous dose is allowed at or before Week 8. No dose adjustments are permitted after the Week 8 visit.

[b]Subjects that will be titrated from 10.0 mg to 20.0 mg must remain on a dose of 15.0 mg for 1 week (ie, at least 4 days) prior to being titrated to 20.0 mg.

An emergency dose reduction blister card will be distributed between trial visits where there is a requested dose titration. The blister card will have sufficient tablets for 7 ± 2 days. If the subject is advised to reduce the IMP due to tolerability issues, the subject will return for an in-clinic visit within 1 week after initiating the dose reduction blister card.

Starting at Week 2, subjects meeting the stabilization criteria (≥ 35% improvement [decrease] of YGTSS TTS) who demonstrate a continued response as described (≥ 35% improvement [decrease] of YGTSS TTS) for 12 consecutive weeks, inclusive, with no more than one excursion of response criteria, will enter the double-blind randomized withdrawal phase. Excursions will not be permitted at the end of the 12th consecutive week of stabilization (ie, the randomization visit). Subjects who experience a second excursion of response criteria should continue in the open-label stabilization phase until they achieve response criteria again, and maintain their response for 12 consecutive weeks with no more than one excursion. Subjects should be discontinued if they no longer have the opportunity to achieve 12 weeks of response in the open-label stabilization phase (eg, the subject has not achieved response by the Week 8 visit).

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3.2.2 Double-blind Randomized Withdrawal Phase

Subjects meeting the stabilization criteria will be randomized in a 1:1:1 ratio to the half-dose arm, full-dose arm, or placebo arm based on their stabilized dose in the open-label stabilization phase. Weight-based dosing will be determined using the body weight measurement from the open-label stabilization phase baseline. See Table 3.2.2-1 for the dosing schedule.

All subjects will take 2 tablets once daily. The 20.0 mg/day dose taken as two 10-mg tablets. No dose adjustments will be allowed in the double-blind randomized withdrawal phase.

Table 3.2.2-1 Double-blind Randomized Withdrawal Phase Doses

Weight Group	Stabilized Dose	Double-blind Randomized Withdrawal Phase Doses		
		Full-dose Arm	Half-dose Arm	Placebo Arm
< 50kg	5 mg	5 mg	2 mg	Matching placebo
	10 mg	10 mg	5 mg	Matching placebo
≥ 50 kg	10 mg	10 mg	5 mg	Matching placebo
	20 mg	20 mg	10 mg	Matching placebo

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

The trial population will include pediatric subjects, 6 to 17 years of age, meeting the current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for TD. It is anticipated that approximately 228 subjects will be enrolled in the open-label stabilization phase from approximately 60 sites worldwide in order to randomize approximately 114 subjects into the double-blind randomized withdrawal phase.

3.3.2 Subject Selection and Numbering

All subjects will be given a unique 5 digit subject screening identification number preceded by an S (SXXXXX).

3.4 Eligibility Criteria

3.4.1 Informed Consent/Informed Assent

Written informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). Consent and assent will be documented on a written informed consent form (ICF) and informed assent form (IAF).

The ICF/IAF will be approved by the same institutional review board/independent ethics committee (IRB/IEC) that approves this protocol. Subjects who are too young to sign an ICF either via wet signature or electronic signature (e-signature) will provide informed assent per local law, and the subject must be able to understand that he or she can withdraw from the trial at any time and for any reason.

Each ICF/IAF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[13] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF/IAF used in the trial before submission to the IRB/IEC. Age-appropriate assent documents will be created and subjects who are able will be required to reconsent or assent as appropriate if they matriculate from one age group to another. Subjects who become legal adults during the trial will be required to provide written informed consent as soon as they reach legal age.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, ICF/IAF must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the subject and/or his/her parent/legal guardian or legally acceptable representative, as applicable by the investigator (or a qualified designee), and it has been documented that the subject and his/her parent/legal guardian or legally acceptable representative has had the opportunity to ask questions, the IRB/IEC-approved written ICF/IAF will be signed and dated by the subject, the subject's legally acceptable representative (eg, guardian) and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The subject will receive a copy of the signed ICF/IAF; the original shall be kept on file by the investigator.

At sites where the electronic ICF application is used, prospective trial participants will be provided with controlled access to the application by trial site staff. When the trial site staff and the participant agree that the participant has enough information to make an informed decision to participate, the participant will electronically sign the ICF or assent form in the electronic ICF application and an electronic date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the ICF and

assent form. Any other parties required by the IRB/IEC (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the electronic ICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied. At sites where the electronic ICF application is not used, paper consent and assent forms will be signed after trial site staff and the participant agree that the participant has enough information to make an informed decision to participate. Any other parties required to provide signatures will also sign the paper forms, and the forms will be stored in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines.

Subjects and his/her parent/legal guardian or legally acceptable representative may be asked to sign additional ICF/IAFs if the protocol is amended to significantly add or change procedures.

Subjects who are not started on treatment after the ICF/IAF is signed are permitted to be rescreened under the conditions specified in Section 3.9 (Screen Failures). In the event that the subject is rescreened for trial participation, a new ICF/IAF must be signed.

If a subject is legally emancipated, informed consent must be sought directly from the subject. Subjects who turn age 18 (or the age of adulthood as specified by local laws or regulations) during the trial must sign a new ICF at that time.

In addition to the English version of the ICF/IAF, the documents may also be translated into local languages for use in this trial. Translation with back-translation for confirmation will be utilized to ensure accuracy.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1.	The subject is a male or female child or adolescent, 6 to 17 years of age (inclusive) at the time of signing the informed consent/assent.
2.	The subject meets current DSM-5 diagnostic criteria for TD, documented at screening and made by an adequately trained clinician, as confirmed by the K-SADS-PL.
3.	The subject has a TTS ≥ 20 on the YGTSS at screening and baseline (Day 1).
4.	The subject, a caregiver, and the investigator must all agree that the presenting tic symptoms cause impairment in the subject's normal routines, which include academic achievement, occupational functioning, social activities, and/or relationships.
5.	Females of childbearing potential (all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started) must have a negative pregnancy test and must not be pregnant or lactating.

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Table 3.4.2-1 Inclusion Criteria	
6.	Written informed consent must be obtained from the subject or a legally acceptable representative (eg, guardian or caregiver), in accordance with the trial site's IRB/IEC and local regulatory requirements, prior to the initiation of any protocol-required procedures. In addition, the subject, as required by the trial site's IRB/IEC, must provide informed assent at screening and as such must be able to understand that he or she can withdraw from the trial at any time.
7.	Ability, in the opinion of the principal investigator, of the subject and the subject's legally acceptable representative (eg, guardian) or caregiver(s) to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, and discontinuation of prohibited concomitant medications, to read and understand the written word in order to complete subject-reported outcomes measures, and to be reliably rated on assessment scales.

K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria	
1.	The subject presents with a clinical presentation and/or history that is consistent with another neurologic condition that may have accompanying abnormal movements. These include, but are not limited to, the following: • Transient tic disorder • Huntington's disease • Parkinson's disease • Sydenham's chorea • Wilson's disease • Mental retardation • Pervasive developmental disorder • Tardive dyskinesia • Traumatic brain injury • Stroke • Restless legs syndrome
2.	The subject has a history of schizophrenia, bipolar disorder, or other psychotic disorder.
3.	The subject has received psychostimulants for the treatment of ADHD and has developed and/or had exacerbations of the tic disorder after the initiation of stimulant treatment. (Note that subjects with ADHD who are treated with psychostimulants and have not developed new tics or a worsening of their current tics can be included if all other enrollment obligations are met).
4.	The subject currently has a primary diagnosis that meets DSM-5 criteria for a mood disorder.
5.	The subject has severe OCD, as evidenced by a CY-BOCS score > 16.
6.	The subject has taken aripiprazole within 1 month (30 days) of the screening visit.
7.	The subject has a history of neuroleptic malignant syndrome.

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Table 3.4.3-1 Exclusion Criteria	
8.	The subject is a sexually active male or FOCBP (all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started) who will not agree to practice 2 acceptable methods of birth control or who will not remain abstinent during the trial and for 30 or 90 days following the last dose of IMP for females and males, respectively. Abstinence will be permitted if it is confirmed and documented at every trial visit. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm with spermicide, intrauterine device, birth control pill, birth control depot injections, implant, condom with spermicide, or sponge with spermicide.
9.	The subject represents a significant risk of committing suicide based on history (suicide attempt in past 1 year), routine psychiatric status examination, investigator's judgment, or who have an answer of "yes" on any question other than 1-3 (current or over the last 30 days) on the baseline/screening version of the C-SSRS.
10.	The subject has a body weight < 16 kg.
11.	Subjects who have taken neuroleptic or antiparkinson drugs within 14 days prior to baseline.
12.	Subjects requiring CBT for TD during the trial period. CBT for other nonexclusionary disorders must remain consistent throughout the trial.
13.	The subject has met DSM-5 criteria for any significant psychoactive substance use disorder within the past 3 months.
14.	A positive drug screen for cocaine, alcohol, or other drugs of abuse (excluding caffeine, nicotine, or prescribed psychostimulants for ADHD). Investigators can choose to repeat a positive drug screen one time during screening period after concurrence from the medical monitor. A second positive test for any drug of abuse would be exclusionary.
15.	Subject requiring medication not allowed per protocol.
16.	Use of any CYP2D6 and CYP3A4 inhibitors or CYP3A4 inducers within 14 days prior to baseline and for the duration of the trial.
17.	Other nutritional or dietary supplements and nonprescription herbal preparations for TD (eg, cannabinoids, N-aceytlcysteine , omega-3 fatty acids, kava extracts, GABA supplements) within 7 days prior to baseline and for the duration of the trial, unless approved in advance by the medical monitor.
18.	The inability to swallow tablets or tolerate oral medication.
19.	Subject has participated in a clinical trial involving either study medication or interventional (non-medication) treatment for TD within the last 60 days.
20.	The following laboratory test results, vital signs and ECG results are exclusionary: a) Platelets ≤ 75,000/mm^3 b) Hemoglobin ≤ 9 g/dL c) Neutrophils, absolute ≤ 1000/mm^3 d) AST > 3 × ULN as defined by the central laboratory e) ALT > 3 × ULN as defined by the central laboratory f) Creatinine ≥ 2 mg/dL g) Diastolic blood pressure > 105 mmHg h) QTc ≥ 450 msec (males) or ≥ 470 msec (females) using the QTcF correction.
	NOTE: In addition, subjects should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which in the investigator's judgment is medically significant and would impact the safety of the subject or the interpretation of the trial results. Criteria are provided in Appendix 1, Appendix 2, and Appendix 3 to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation. Abnormal results for laboratory parameters or vital signs should be repeated once to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. Based on the QTcF correction, a subject will be excluded if the correction exceeds 450 msec (males) or ≥ 470 msec (females).

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ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBT = cognitive-behavioral therapy; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; CYP = cytochrome P450; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FOCBP = female of childbearing potential; OCD = obsessive-compulsive disorder; QTc = corrected QT interval; QTcF = corrected QT interval for heart rate using Fridericia's formula; ULN = upper limit of normal.

Subjects must agree to restrictions to medications and lifestyle as described in Section 4.

3.5 Endpoints

3.5.1 Efficacy Endpoints

3.5.1.1 Primary Endpoint

The primary efficacy endpoint is the time from randomization to relapse during the double-blind randomized withdrawal phase.

3.5.1.2 Secondary Endpoint

Not applicable.

3.5.1.3 Exploratory Efficacy Endpoint(s)

The other efficacy endpoints include the following:

- Mean change from randomization to last visit (Week 12 for completers and withdrawal visit for discontinued subject) in YGTSS TTS score
- Mean change from randomization to last visit (Week 12 for completers and withdrawal visit for discontinued subject) in Total YGTSS score
- Mean change from randomization to last visit (Week 12 for completers and withdrawal visit for discontinued subject) in CGI-TS Severity score
- CGI-TS Improvement score at last visit (Week 12 for completers and withdrawal visit for discontinued subject)

3.5.2 Safety Endpoint(s)

Safety endpoints include the following:

- Adverse events (AEs)
- Laboratory tests (hematology, serum chemistry [including prolactin (blinded), glycosylated hemoglobin, and thyroid-stimulating hormone (TSH)], urinalysis, and urine pregnancy tests)
- Vital signs
- Electrocardiograms (ECGs)

- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Simpson-Angus Scale (SAS)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Body weight
- Body mass index (BMI)
- Waist circumference

3.6 Measures to Minimize/Avoid Bias

3.6.1 Randomization

Subjects will be randomly assigned in a 1:1:1 ratio via interactive response technology (IRT) to the half-dose aripiprazole arm, full-dose aripiprazole arm, or placebo arm. The randomization will be stratified by region and weight group, where region is classified as North America (including USA and Canada) vs. Rest of the World and weight group is classified as low weight (body weight at Baseline < 50 kg) vs. high weight (body weight at Baseline ≥ 50 kg). Computer-generated randomization codes will be prepared by a sponsor's independent biostatistician.

3.6.2 Blinding

Placebo tablets are identical in appearance to active IMP and all dose strength aripiprazole tablets are visually indistinguishable.

Except in cases of emergency unblinding, subjects, investigational site personnel, Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) employees, and all other trial personnel will remain blinded to the identity of the treatment assignments until every subject has completed trial treatment and the database has been locked.

3.7 Trial Procedures

The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 3 years and 4 months including an estimated 30-month recruitment period.

Individual participation for subjects who complete the trial can range from a minimum of approximately 30 weeks to approximately 42 weeks. Length of participation will vary, depending on the screening duration (3 - 42 days).

However, the trial may be terminated early based on the result of a planned interim analysis (IA).

During the open-label stabilization phase, visits will occur at Week 1 (± 2 days) for the titration visit and at Weeks 2, 3, and 4 (± 2 days) and Weeks 6, 8, 10, 12, 14, 16, 18, and 20 (± 3 days). Upon entering the double-blind randomized withdrawal phase, subjects will be randomized to aripiprazole full dose, aripiprazole half dose, or placebo. Subjects will have trial visits at Weeks 1, 2, 3, and 4 (± 2 days) and Weeks 6, 8, 10, and 12 (± 3 days).

Screening assessments may occur during 1 or more visits (as needed), and must occur in the clinic. The baseline visit will occur in the clinic, as well the open-label stabilization phase visits on Weeks 1, 2, 4, 8, 12, 14, 16, 18, and 20 and the double-blind, randomized withdrawal phase visits at Weeks 1, 2, 4, 8, and 12. All other visits will occur via telephone with direct patient visualization (except for open-label Week 3 which does not require direct patient visualization), web, in-clinic, or other acceptable means of contact. Trial assessment time points are summarized by phase in Table 3.7-1 (Pretreatment and Open-label Stabilization Phase) and Table 3.7-2 (Double-blind Randomized Withdrawal Phase).

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Table 3.7-1 Schedule of Assessments - Screening and Open-label Stabilization Phase

Assessments/Procedures	Screening and Washout Period (Days −42 to −3)	Open-label Stabilization Phase Visits - Week (Day)[a]												
		Baseline (Day 1)	1 (8 ± 2)	2 (15 ± 2)	3 (22 ± 2)	4 (29 ± 2)	6 (43 ± 3)	8 (57 ± 3)	10 (71 ± 3)	12 (85 ± 3)	14 (99 ± 3)	16 (113 ± 3)	18 (127 ± 3)	20 (141 ± 3)/ EOP or ET[b]
Screening/Eligibility														
Informed Consent/Assent[c]	X													
Confirmation of diagnosis of TD by DSM-5[d]	X													
K-SADS-PL[e]	X													
CY-BOCS[f]	X													
Inclusion/exclusion criteria	X	X												
Demography	X													
Medical history	X													
Psychiatric history	X													
Record current psychotropic therapy[g]	X	X	X	X		X	X	X	X	X	X	X	X	X
Washout of prohibited medications, including psychotropics[g]	X													
Trial Assessments														
YGTSS[f]	X	X	X	X		X	X	X	X	X	X	X	X	X
CGI-TS Severity[f]	X	X	X	X		X	X	X	X	X	X	X	X	X
CGI-TS Improvement[f]			X	X		X	X	X	X	X	X	X	X	X
C-SSRS (children's version)[f,h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Table 3.7-1 Schedule of Assessments - Screening and Open-label Stabilization Phase

Assessments/Procedures	Screening and Washout Period (Days −42 to −3)	Open-label Stabilization Phase Visits - Week (Day)[a]												
		Baseline (Day 1)	1 (8 ± 2)	2 (15 ± 2)	3 (22 ± 2)	4 (29 ± 2)	6 (43 ± 3)	8 (57 ± 3)	10 (71 ± 3)	12 (85 ± 3)	14 (99 ± 3)	16 (113 ± 3)	18 (127 ± 3)	20 (141 ± 3)/ EOP or ET[b]
Physical examination	X							X[i]						X
Height	X	X						X				X		X
Body weight	X	X				X		X		X		X		X
Waist circumference	X	X				X		X		X		X		X
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[k]	X							X[i]						X
Clinical laboratory tests (hematology, serum chemistry, and urinalysis)[l]	X							X[i]						X
Glycosylated hemoglobin, prolactin (blinded),TSH[l,m]	X							X[i]						X
Urine pregnancy test[n]	X	X				X		X		X		X		X
Documentation of birth control status[o]	X	X	X	X		X	X	X	X	X	X	X	X	X
Urine drug and blood alcohol screen[p]	X							X						X
SAS[f]	X	X						X						X
AIMS[f]	X	X						X						X
BARS[f]	X	X						X						X
Adverse Events[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Table 3.7-1 Schedule of Assessments - Screening and Open-label Stabilization Phase

Assessments/Procedures	Screening and Washout Period (Days −42 to −3)	Open-label Stabilization Phase Visits - Week (Day)[a]												
		Baseline (Day 1)	1 (8 ± 2)	2 (15 ± 2)	3 (22 ± 2)	4 (29 ± 2)	6 (43 ± 3)	8 (57 ± 3)	10 (71 ± 3)	12 (85 ± 3)	14 (99 ± 3)	16 (113 ± 3)	18 (127 ± 3)	20 (141 ± 3)/ EOP or ET[b]
Prior and Concomitant Medications[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Management														
Dispense IMP		X	X	X		X		X[s]		X[s]		X[s]		X[t]
Assess eligibility for treatment	X	X												
Assess stabilization criteria				X		X	X	X	X	X	X	X	X	X
Randomization of stable subjects											X[u]	X[u]	X[u]	X[t]
Drug accountability		X	X	X		X		X		X		X		X
Phone call to assess if titration is needed in-clinic					X									

D = day; EOP = end of phase; IRE = immediately reportable event; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version.

[a]The subject will return to the clinic for visits at Weeks 2 (± 2 days), 4 (± 2 days), 8 (± 3 days), 12 (± 3 days), 14 (± 3 days), 16 (± 3 days), and 18 (± 3 days). The Week 20 (± 3 days)/EOP visit will also occur in the clinic. All other visits during the open-label stabilization phase will occur via telephone with direct patient visualization (except for open-label Week 3 which does not require direct patient visualization), web, in-clinic, or other acceptable means of contact.

[b]The End of Phase visit must serve as the baseline for double-blind randomized withdrawal phase; therefore, all evaluations noted for "Week 20 (141)/EOP or early termination (ET)" must be performed on the day of randomization prior to the first dose of double-blind IMP. Please note that randomization must occur on the same day that the subject receives double-blind IMP for double-blind randomized withdrawal phase. For subjects who meet the 12-week (eg, 6 bi-weekly-visits) stabilization requirement at a visit that coincides with IMP dispensing, the "Week 20 (141)/ EOP or ET" evaluations will be performed instead of the evaluations noted for the individual trial visit. Once these evaluations are completed, the subject will be randomized and dispensed double-blind IMP.

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[c]Informed consent/assent must be obtained from all legally acceptable representatives/subjects prior to initiation of any trial-related procedures.

[d]Current diagnosis of TD should be made and documented at screening by an adequately qualified clinician.

[e]K-SADS-PL: This assessment must be performed by certified personnel.

[f]Benztropine (up to 4 mg/day) is not to be administered 12 hours prior to rating scales. Benzodiazepines (up to 3 mg/day lorazepam equivalents) are not to be administered 4 hours prior to rating scales.

[g]Tapering rates for washout medications are at the discretion of the investigator and are to be determined on an individual basis, with consideration to subject state, dose, and known PK of the medication being tapered, as long as the protocol-mandated discontinuation timeframe is met. The exception is a long-acting depot medication, which cannot be tapered and will be discontinued after informed consent/assent is obtained. See Section 4.1 for additional details.

[h]The C-SSRS (children's version) will be completed for all subjects at screening and at all subsequent visits.

[i]ET procedures performed only on subjects not starting to meet stability at the open-label stabilization phase Week 8 visit and subjects not maintaining stability by the open-label stabilization phase Week 20 visit. These subjects will be discontinued from the trial.

[j]Vital signs include systolic and diastolic blood pressure and heart rate and will be performed at all in-clinic visits. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been sitting for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes. If a remote visit is converted to an in-clinic visit, vital signs will be recorded. Vital signs will not be collected for remote visits that are not converted to occur in-clinic.

[k]A standard 12-lead ECG will be performed at rest after the subject has been lying down for approximately 5 minutes. ECGs will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety. Based on the QTcF, a subject will be excluded if the correction is ≥ 450 msec (males) or ≥ 470 msec (females). Subjects with clinically significant ECG findings at screening may enter the open-label stabilization phase only after the screening ECG is repeated and determined by the investigator prior to treatment to have no abnormality(ies) that are clinically significant.

[l]Subjects should fast for a minimum of 8 hours prior to blood draws for all laboratory assessments. If nonfasting blood samples are obtained initially for determining eligibility for the trial, a fasting blood sample should be drawn prior at or prior to the baseline visit (prior to the first dose of open-label drug). Subjects with clinically significant abnormal laboratory test results at screening may enter the open-label stabilization phase only after repeated laboratory test results are received and determined by the investigator prior to treatment to have no abnormality(ies) that are clinically significant.

[m]If the observed TSH level is outside of the normal range, tests of triiodthyronine (T3) and thyroxine (T4) levels will be assessed.

[n]A urine pregnancy test will be performed at screening on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started. Subjects with a positive result will be excluded from the trial. Urine pregnancy tests can be performed at any point during the trial if pregnancy is suspected. All positive urine pregnancy test results must be confirmed by a serum test. Subjects who are taking IMP and have a positive urine and serum pregnancy test must discontinue treatment, be withdrawn from the trial, and an immediately reportable event (IRE) form should be completed.

[o]Abstinence will be permitted if it is confirmed and documented at every trial visit.

[p]A urine drug screen and a blood alcohol test, is required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator. Subjects who have 2 positive drug screens for any drug of abuse (with the exception of caffeine, nicotine, or prescribed psychostimulants for ADHD) at any time during the trial must be discontinued from the trial.

[q]Adverse events will be recorded starting at the time the ICF/IAF is signed.

[r]A complete history of use of central nervous system (CNS)-active compounds other than neuroleptics will be recorded, as will all other medications taken within 30 days of starting IMP. In addition, all prescription and nonprescription medications taken during the trial will be recorded as concomitant medications.

[s]Only subjects starting to meet stability (eg, ≥ 35% improvement [decrease] of YGTSS TTS) by the open-label stabilization phase Week 8 visit will be allowed to continue in the open-label stabilization phase and have IMP dispensed. Any subject not starting to show stability by the open-label stabilization phase Week 8 visit will be discontinued from the trial and will undergo ET procedures.

[t]Only subjects who have met stability criteria for 12 consecutive weeks with no more than 1 excursion of the stabilization criterion at the open-label stabilization phase Week 20 visit and who will continue into the double-blind randomized withdrawal phase and have IMP dispensed.

[u]Subjects meeting stability for 12 consecutive weeks with no more than 1 excursion of the stabilization criterion will continue into the double-blind randomized withdrawal phase with IMP being dispensed. Excursions are not permitted at the end of the 12th consecutive week of stabilization (ie, the randomization visit).

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Table 3.7-2 Schedule of Assessments - Double-blind Randomized Withdrawal Phase

Assessments/Procedures	Double-blind Randomized Withdrawal Phase[a]								Follow-up Period 30 Days (+ 3 days)
	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 6 (± 3 days)	Week 8 (± 3 days)	Week 10 (± 3 days)	Week 12 (± 3 days)/ ET	
Trial Assessments									
Record current psychotropic therapy	X	X	X	X	X	X	X	X	X
YGTSS[b]	X	X	X	X	X	X	X	X	
CGI-TS Severity[b]	X	X	X	X	X	X	X	X	
CGI-TS Improvement[b]	X	X	X	X	X	X	X	X	
C-SSRS (children's version)[b]	X	X	X	X	X	X	X	X	
Physical examination								X	
Height								X	
Body weight				X				X	
Waist circumference				X				X	
Vital signs[c]	X	X	X	X	X	X	X	X	
12-lead ECG[d]				X				X	
Clinical laboratory tests (hematology, serum chemistry, urinalysis)[e]				X				X	
Glycosylated hemoglobin, prolactin (blinded), TSH[e,f]				X				X	
Urine pregnancy test[g]		X		X		X		X	
Documentation of birth control status[h]	X	X	X	X	X	X	X	X	
Urine drug and blood alcohol screen[i]				X				X	
SAS[b]	X			X				X	

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Table 3.7-2 Schedule of Assessments - Double-blind Randomized Withdrawal Phase

Assessments/Procedures	Double-blind Randomized Withdrawal Phase[a]								Follow-up Period 30 Days (+ 3 days)
	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 6 (± 3 days)	Week 8 (± 3 days)	Week 10 (± 3 days)	Week 12 (± 3 days)/ ET	
AIMS[b]	X			X				X	
BARS[b]	X			X				X	
Adverse Events[j]	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications[k]	X	X	X	X	X	X	X	X	X
Trial Management									
Dispense IMP	X	X		X		X			
Drug accountability	X	X		X		X		X	

[a]After randomization, the subject will return to the clinic for weekly then bi-weekly visits at Weeks 1 (± 2 days), 2 (± 2 days), 4 (± 2 days), and 8 (± 3 days) during the double blind randomized withdrawal phase. Visits at Weeks 3 (± 2 days), 6 (± 3 days), and 10 (± 3 days) will occur via telephone with direct patient visualization, web, in-clinic, or other acceptable means of contact. If the subject terminates early from the trial, the end-of-treatment visit procedures should be completed.

[b]Benztropine (up to 4 mg/day) is not to be administered 12 hours prior to rating scales. Benzodiazepines (up to 3 mg/day lorazepam equivalents) are not to be administered 4 hours prior to rating scales.

[c]Vital signs include systolic and diastolic blood pressure and heart rate and will be performed at all in-clinic visits. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been sitting for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes. If a remote visit is converted to an in-clinic visit, vital signs will be recorded. Vital signs will not be collected for remote visits that are not converted to occur in-clinic.

[d]A standard 12-lead ECG will be performed at rest after the subject has been lying down for approximately 5 minutes. ECGs will be evaluated at the investigational site to monitor safety.

[e]Subjects should fast for a minimum of 8 hours prior to blood draws for all laboratory assessments.

[f]If the observed TSH level is outside of the normal range, tests of triiodthyronine (T3) and thyroxine (T4) levels will be assessed.

[g]Urine pregnancy tests can be performed at any point during the trial if pregnancy is suspected. All positive urine pregnancy test results must be confirmed by a serum test. Treated subjects with a positive urine and serum pregnancy test must discontinue treatment, be withdrawn from the trial, and an IRE form should be completed.

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[h]Abstinence will be permitted if it is confirmed and documented at every trial visit.

[i]A urine drug screen and a urine blood test can be conducted at any time during the trial at the discretion of the investigator. Subjects who have 2 positive drug screens for any drug of abuse (with the exception of caffeine, nicotine, or prescribed psychostimulants for ADHD) at any time during the trial must be discontinued.

[j]Adverse events will be recorded starting at the time the ICF/IAF is signed.

[k]All prescription and nonprescription medications taken during the trial will be recorded as concomitant medications.

3.7.1 Schedule of Assessments

3.7.1.1 Pretreatment Phase: Screening and Washout Period

This phase includes both a screening and washout period. Screening and washout (if required) will take place between Days −42 and −3 prior to enrollment. Screening assessments may occur during 1 or more visits (as needed), and must occur in the clinic.

The following procedures will be conducted during the screening period for all subjects:

1) Subjects and the subject's legally acceptable representative (eg, guardian) will sign an ICF/IAF to participate in this trial prior to initiation of any trial-related procedures. After signing the ICF/IAF, subjects will be assigned a unique subject screening identification number through the eConsent system that is transferred to both the eSource and IRT.
2) Trial personnel will enter subject data into eSource to register all trial visits (screening visit only).
3) The DSM-5 diagnosis of TD will be confirmed and documented by an adequately trained clinician.
4) After TD is documented, the investigator (or qualified designee) will administer the Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (K-SADS-PL) to confirm the diagnosis. The K-SADS-PL must be administered by an adequately trained clinician.
5) Completion of the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). Subject must have a score ≤ 16 to qualify for the trial.
6) An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
7) Demographic data and full medical and psychiatric history will be recorded.
8) Current psychotropic therapy will be recorded.
9) A complete history of use of central nervous system (CNS)-active compounds other than neuroleptics will be recorded, including details (eg, drug name, dose, and frequency), as will all other medications taken within 30 days of starting IMP. In addition, all prescription and nonprescription medications taken during the screening period will be recorded as concomitant medications.
10) The YGTSS and CGI-TS Severity will be performed to assess symptoms associated with TD. Subjects are required to have a TTS ≥ 20 on the YGTSS at screening and baseline in order to be included in the trial.
11) Completion of the C-SSRS (children's version).
12) The SAS, BARS, and AIMS will be administered. Benztropine (up to 4 mg/day) is not to be administered 12 hours prior to rating scales. Benzodiazepines (up to 3 mg/day lorazepam equivalents) are not to be administered 4 hours prior to rating scales.
13) A complete physical examination will be performed.

14) Body weight, height, and waist circumference will be measured. Subjects with body weight < 16 kg will be excluded from the trial.
15) Vital signs including systolic and diastolic blood pressure and heart rate will be measured. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been sitting for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes.
16) A standard 12-lead ECG will be performed at rest after the subject has been lying down for approximately 5 minutes. ECGs will be evaluated at the investigational site to determine the subject's eligibility. Based on the corrected QT interval for heart rate using Fridericia's formula (QTcF), a subject will be excluded if the correction is ≥ 450 msec (males) or ≥ 470 msec (females). Subjects with clinically significant ECG findings at screening may enter the open-label stabilization phase only after the screening ECG is repeated and determined by the investigator prior to treatment to have no abnormality(ies) that are clinically significant.
17) Fasting blood samples will be collected for clinical laboratory tests (hematology and serum chemistry, including TSH, glycosylated hemoglobin, and prolactin levels; prolactin samples will remain blinded). Subjects should fast for a minimum of 8 hours prior to blood draws for all laboratory assessments; however, a subject should provide informed consent for the trial prior to being asked to fast for blood draws. If nonfasting blood samples are obtained initially for determining eligibility for the trial, a fasting blood sample should be drawn at or prior to the baseline visit (prior to the first dose of open-label drug). Subjects with clinically significant abnormal laboratory test results at screening may enter the open-label stabilization phase only after repeated laboratory test results are received and determined by the investigator prior to treatment to have no abnormality(ies) that are clinically significant. If the observed TSH level is outside the normal range, a test of T3 and T4 levels will be performed.
18) Urine will be collected for urinalysis and urine screen(s) for drugs of abuse and a blood sample will be taken for alcohol.
19) A urine pregnancy test will be done on females of childbearing potential (FOCBP). Subjects with a positive result will be excluded from the trial. If positive, a follow-up serum pregnancy test will be performed and the subject will not be assigned to treatment.
20) For all FOCBP and sexually active males, documentation of birth control methods will be completed. Abstinence is permitted if it is confirmed and documented at every visit.
21) AEs will be recorded starting at the time the ICF/IAF is signed.

Subject who satisfy eligibility criteria and do not require washout from prohibited medications can enter the open-label stabilization phase directly.

Subjects who require medication washout will undergo the following procedures during the washout period:

1) Washout from prohibited medications, including psychotropics, will begin, if applicable. Tapering rates for washout medications are at the discretion of the investigator and are to be determined on an individual basis, with consideration to subject state, dose, and known PK of the medication being tapered, as long as the protocol-mandated discontinuation timeframe is met. The exception is a long-acting depot medication, which cannot be tapered and would be discontinued after the informed consent is obtained. All psychotropic medications and any medications used to treat tics must be discontinued for at least 2 weeks (14 days) prior to the baseline visit, with the exception of psychostimulant medications such as, but not limited to, Vyvanse, Adderall, Concerta, Metadate CR, Ritalin LA, Focalin, and Focalin XR, prescribed for the treatment of symptoms of ADHD, which are permitted during the trial. Use of psychostimulant medications is only permitted if the subject did not develop and/or have an exacerbation of the tic disorder after the initiation of treatment with the psychostimulant. In addition, the dose of any psychostimulant must have been stable for at least 4 weeks prior to screening. All SSRIs/SNRIs must be discontinued at least 4 weeks (28 days) prior to the baseline visit. In addition, long-acting (depot) neuroleptics must be discontinued for at least 1 full cycle (2 weeks to 1 month, depending on the drug) plus 2 weeks prior to the baseline visit. Clonidine, guanfacine, guanabenz, atomoxetine and carbamazepine are prohibited during the trial and must be discontinued for at least 2 weeks prior to the baseline visit. Subjects must have discontinued aripiprazole treatment at least 30 days prior to the screening visit. Subjects not in need of medication washout may proceed to the trial baseline visit after the inclusion/exclusion criteria have been met.
2) AEs will be recorded starting at the time the ICF/IAF is signed.
3) All prescription and nonprescription medications taken during the washout period will be recorded as concomitant medications.

3.7.1.2 Baseline Visit (Day 1)

If the subject is found to be eligible for the trial during the screening period and has either completed or does not require the washout of previous designated medications, the subject will return to clinic for the baseline (Day 1) visit of the open-label stabilization phase. The following procedures are to be completed prior to dosing:

1) Subject eligibility will be confirmed.
2) Current psychotropic therapy will be recorded.

3) The YGTSS and CGI-TS severity will be performed to assess symptoms associated with TD. Subjects are required to have a TTS ≥ 20 on the YGTSS at screening and baseline in order to be included in the trial.
4) Completion of the C-SSRS (children's version).
5) The SAS, BARS, and AIMS will be administered. Benztropine (up to 4 mg/day) is not to be administered 12 hours prior to rating scales. Benzodiazepines (up to 3 mg/day lorazepam equivalents) are not to be administered 4 hours prior to rating scales.
6) Height, body weight, and waist circumference will be measured.
7) Vital signs include systolic and diastolic blood pressure and heart rate will be measured. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been sitting for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes.
8) A urine pregnancy test will be done on all FOCBP. If the results of the test are positive, then a serum pregnancy test will be completed.
9) For all FOCBP and sexually active males, documentation of birth control methods will be completed. Abstinence is permitted if it is confirmed and documented at every visit.
10) AEs and concomitant medications will be recorded.

Confirmation that all inclusion and exclusion criteria were evaluated to ensure subject eligibility was met. If the subject still meets all inclusion/exclusion criteria, the following tasks will be completed:

1) Subjects will be dispensed IMP and administered the first dose while in the clinic. Subjects will take each daily dose of IMP at approximately the same time each day. The date and time of the first dose will be recorded in the eSource.
2) The investigator will schedule the Week 1 visit for within 7 days ± 2 days.

3.7.1.3 Open-label Stabilization Phase Titration Visit (Week 1)

The subject will return to the clinic at Week 1 (± 2 days) during the open-label stabilization phase. The following procedures are to be completed:

1) Current psychotropic therapy will be recorded
2) The YGTSS and CGI-TS (both the severity and improvement scales) will be performed to assess symptoms associated with TD.
3) Completion of the C-SSRS (children's version).
4) Vital signs including systolic and diastolic blood pressure and heart rate will be measured. Orthostatic assessments of blood pressure and heart rate will be made

after the subject has been sitting for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes.

5) For all FOCBP and sexually active males, documentation of birth control methods will be completed. Abstinence is permitted if it is confirmed and documented at every visit.
6) AEs and concomitant medications will be recorded.
7) The subject will be dispensed once-daily IMP. The subject will be dosed in the clinic unless the evening dosing is preferred. Subjects will be instructed to return unused IMP at the next scheduled office visit.
8) Drug accountability records will be completed.

3.7.1.4 Open-label Stabilization Phase Stabilization Visits

The subject will return to the clinic for visits at Weeks 2 (± 2 days) and 4 (± 2 days) and visits at Weeks 8 (± 3 days), 12 (± 3 days), 14 (± 3 days), 16 (± 3 days), and 18 (± 3) days to start assessment of stability. The Week 20 (± 3 days)/EOP visit will also occur in the clinic. All other visits during the open-label stabilization phase (ie, Weeks 3, 6, and 10) will occur via telephone with direct patient visualization (except for Week 3 which does not require direct patient visualization), web, in-clinic, or other acceptable means of contact. The following procedures are to be completed at each visit:

1) Current psychotropic therapy will be recorded at all open-label visits EXCEPT for Week 3.
2) The YGTSS and CGI-TS (both the severity and improvement scales) will be performed to assess symptoms associated with TD at all open-label visits EXCEPT for Week 3.
3) Completion of the C-SSRS (children's version).
4) For all FOCBP and sexually active males, documentation of birth control methods will be completed at all open-label visits EXCEPT for Week 3. Abstinence is permitted if it is confirmed and documented at every visit.
5) AEs and concomitant medications will be recorded.
6) Stability will be assessed at all open-label visits EXCEPT for Week 3.

The following procedures will be performed at the Weeks 2 (± 2 days), 4 (± 2 days), 8 (± 2 days), 12 (± 3 days), 14 (± 3 days), 16 (± 3 days), and 18 (± 3 days) visits only:

1) Vital signs including systolic and diastolic blood pressure and heart rate will be measured. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been sitting for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes. If visits on Weeks 3, 6, and/or 10 are converted to in-clinic visits, vital signs will

be recorded. Vital signs will not be collected for remote visits that are not converted to occur in-clinic.

2) The subject will be dispensed once daily IMP. The subject will be dosed in the clinic unless the evening dosing is preferred. Subjects will be instructed to return unused IMP at the next scheduled office visit.
3) Drug accountability records will be completed.

The following procedures will be performed at the Weeks 4 (± 2 days), 8 (± 3 days), 12 (± 3 days), and 16 (± 3 days) visits only:

1) Body weight and waist circumference will be measured.
2) A urine pregnancy test will be done on all FOCBP, but can be done at any visit is pregnancy is suspected.

The following procedures will be performed at the Week 8 (± 3 days) visit only:

1) A complete physical examination will be performed.
2) The SAS, BARS, and AIMS will be administered. Benztropine (up to 4 mg/day) is not to be administered 12 hours prior to rating scales. Benzodiazepines (up to 3 mg/day lorazepam equivalents) are not to be administered 4 hours prior to rating scales.
3) A standard 12-lead ECG will be performed at rest after the subject has been lying down for approximately 5 minutes.
4) Fasting blood samples will be collected for clinical laboratory tests (hematology and serum chemistry, including TSH, glycosylated hemoglobin, and prolactin levels; prolactin samples to remain blinded). If the observed TSH level is outside the normal range, a test of T3 and T4 levels will be performed.
5) Urine will be collected for urinalysis and urine screen(s) for drugs of abuse and a blood sample will be taken for alcohol.

The following procedure will be performed at the Weeks 8 (± 3 days) and 16 (± 3 days) visits only:

1) Height will be measured.

3.7.1.5 Open-label Stabilization Phase Contact (Week 3)

The Week 3 (± 2 days) contact will consist of telephone contact to assess any AEs experienced since the last trial visit and information on ongoing AEs and serious TEAEs and recording of concomitant medications, including current psychotropic therapy.

If the investigator feels that a dose titration is required the subject will return to the clinic for IMP dispensing. The following procedures are to be completed at this visit:

1) Current psychotropic therapy will be recorded.
2) Completion of the C-SSRS (children's version).
3) AEs and concomitant medications will be recorded.
4) If visit is converted to an in-clinic visit, vital signs will be recorded. Vital signs including systolic and diastolic blood pressure and heart rate will be measured. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been sitting for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes.

3.7.1.6 Open-label Stabilization Phase /Randomization/Early Termination

Subjects should be randomized at the visit where they meet the protocol-specified stabilization criteria; the visit where stabilization is confirmed will revert to the EOP visit. However, if for some reason subject was not randomized, if the subject still meets eligibility criteria at the next visit they can be randomized at that time. In those instances, the earlier assessment should be completed according to that week's required assessments, and not as an EOP visit.

The subject will return to the clinic for a visit at Week 20 (± 3 days) during the open-label stabilization phase. Investigators must perform the open-label stabilization phase assessments to determine if the subject has maintained the stabilization criteria for entry into the double-blind randomized withdrawal phase. The EOP visit must serve as the baseline for double-blind randomized withdrawal phase; therefore, all evaluations noted for Week 20/EOP or ET must be performed on the day of randomization prior to the first dose of double-blind IMP. Randomization (Section 3.7.1.6.1) must occur on the same day that the subject receives double-blind IMP for double-blind randomized withdrawal phase.

The following procedures are to be completed at the Week 20/EOP visit:

1) Current psychotropic therapy will be recorded.
2) The YGTSS and CGI-TS (severity and improvement assessments) will be performed to assess symptoms associated with TD.
3) Completion of the C-SSRS (children's version).
4) For all FOCBP and sexually active males, documentation of birth control methods will be completed. Abstinence is permitted if it is confirmed and documented at every visit.

5) AEs and concomitant medications will be recorded.
6) Drug accountability records will be completed.
7) Stability will be assessed.
8) A complete physical examination will be performed.
9) Height, body weight, and waist circumference will be measured.
10) A urine pregnancy test will be done on FOCBP.
11) Urine drug and blood alcohol screens will be done.
12) The SAS, BARS, and AIMS will be administered. Benztropine (up to 4 mg/day) is not to be administered 12 hours prior to rating scales. Benzodiazepines (up to 3 mg/day lorazepam equivalents) are not to be administered 4 hours prior to rating scales.
13) Vital sign measurements (systolic and diastolic blood pressure and heart rate) will be recorded. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been sitting for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes.

Subjects that have not maintained stability for 12 consecutive weeks in the open-label stabilization phase can continue the bi-weekly visits to assess stability. Subjects should be discontinued (see Section 3.7.1.6.2) if they no longer have the opportunity to achieve 12 weeks of stability in the open-label stabilization phase (eg, the subject has not achieved response by Week 8). The following procedures are to be completed at each visit:

1) The subject will be dispensed once-daily IMP, if continuing in the trial. The subject will be dosed in the clinic unless the evening dosing is preferred. Subjects will be instructed to return unused IMP at the next scheduled office visit. For details regarding those subjects who are discontinued from the trial, refer to Section 3.7.1.6.2.

3.7.1.6.1 Randomization

Subjects that have maintained stability for 12 consecutive weeks with no more than 1 excursion of the stabilization criterion will enter the double-blind randomized withdrawal phase. The following randomization procedures will be completed at this visit:

1) A standard 12-lead ECG will be performed at rest after the subject has been lying down for approximately 5 minutes.
2) Fasting blood samples will be collected for clinical laboratory tests (hematology and serum chemistry, including TSH, glycosylated hemoglobin, and prolactin

levels; prolactin samples to remain blinded). If the observed TSH level is outside the normal range, a test of T3 and T4 levels will be performed.

3) Urine will be collected for urinalysis.
4) Subjects should be dispensed IMP and administered the first dose while in the clinic unless evening dose is preferred. Subjects will take each daily dose of IMP at approximately the same time each day. All other assessments should be completed prior to the administration of IMP.
5) The investigator will schedule the visit for the double-blind randomized withdrawal phase Week 1 visit for within 7 days ± 2 days.

3.7.1.6.2 Open-label Stabilization Phase/Early Termination

Subjects who have never met stability criteria by the Week 8 visit, or subjects who have not met stability criteria for 12 consecutive weeks (with 1 excursion permitted) by Week 20 will be discontinued from the trial after completion of ET procedures. Subjects who discontinue early should also complete the 30-day follow-up visit as described in Section 3.7.1.9. For subjects who discontinue early, attempts should be made to complete ALL evaluations, particularly efficacy assessments (ie, YGTSS and CGI-TS), for the open-label stabilization phase visit/ET visit prior to the administration of any new psychotropic medications. However, if the subject receives a new antipsychotic prior to ET procedures, no efficacy assessments should be done. Any prohibited medications started before the end of the trial assessments should be documented as a protocol deviation in the source notes. The following additional ET activities and assessments will occur at the open-label stabilization phase visit (or at ET visit, if applicable):

1) A complete physical examination will be performed.
2) Height, body weight, and waist circumference will be measured.
3) A standard 12-lead ECG will be performed at rest after the subject has been lying down for approximately 5 minutes.
4) Fasting blood samples will be collected for clinical laboratory tests (hematology and serum chemistry, including TSH, glycosylated hemoglobin, and prolactin levels; prolactin samples to remain blinded). If the observed TSH level is outside the normal range, a test of T3 and T4 levels will be performed.
5) Urine will be collected for urinalysis.
6) A urine pregnancy test will be done on all FOCBP.
7) For all FOCBP and sexually active males, documentation of birth control methods will be completed.

3.7.1.7 Double-blind Randomized Withdrawal Phase Visits

After randomization, the subject will return to the clinic for weekly then bi-weekly visits at Weeks 1 (± 2 days), 2 (± 2 days), 4 (± 2 days), and 8 (± 3 days) during the double-blind randomized withdrawal phase. Visits at Weeks 3 (± 2 days), 6 (± 3 days), and 10 (± 3 days) will occur via telephone with direct patient visualization, web, in-clinic, or other acceptable means of contact. If the subject terminates early from the trial, the end-of-treatment visit procedures should be completed.

The following procedures are to be completed at each visit:

1) Current psychotropic therapy will be recorded.
2) The YGTSS and CGI-TS (both the severity and improvement scales) will be performed to assess symptoms associated with TD.
3) Completion of the C-SSRS (children's version).
4) For all FOCBP and sexually active males, documentation of birth control methods will be completed. Abstinence is permitted if it is confirmed and documented at every visit.
5) AEs and concomitant medications will be recorded.

The following procedures will be performed at the Weeks 1 (± 2 days), 2 (± 2 days), 4 (± 2 days), and 8 (± 3 days) visits only:

1) Vital signs including systolic and diastolic blood pressure and heart rate will be measured. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been sitting for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes. If visits on Weeks 3, 6, and/or 10 are converted to in-clinic visits, vital signs will be recorded. Vital signs will not be collected for remote visits that are not converted to occur in-clinic.
2) The subject will be dispensed once-daily IMP. The subject will be dosed in the clinic unless the evening dosing is preferred. They will be instructed to return the medication at the next scheduled office visit.
3) Drug accountability records will be completed.

The following procedures will be performed at the Week 2 (± 2 days), 4 (± 2 days), and 8 (± 3 days) visits only:

1) A urine pregnancy test will be done on all FOCBP.

The following procedures will be performed at the Week 1 (± 2 days) and 4 (± 2 days) visits only:

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1) The SAS, BARS, and AIMS will be administered. Benztropine (up to 4 mg/day) is not to be administered 12 hours prior to rating scales. Benzodiazepines (up to 3 mg/day lorazepam equivalents) are not to be administered 4 hours prior to rating scales.

The following procedures will be performed at the Week 4 (± 2 days) visit only:

1) Body weight and waist circumference will be measured.
2) A standard 12-lead ECG will be performed at rest after the subject has been lying down for approximately 5 minutes.
3) Fasting blood samples will be collected for clinical laboratory tests (hematology and serum chemistry, including TSH, glycosylated hemoglobin, and prolactin levels; prolactin samples to remain blinded). If the observed TSH level is outside the normal range, a test of T3 and T4 levels will be performed.
4) Urine will be collected for urinalysis and urine screen(s) for drugs of abuse and a blood sample will be taken for alcohol.

3.7.1.8 Double-blind Randomized Withdrawal Phase Week 12 or Early Termination

One day before the Week 12 (± 3 days) visit of the double-blind randomized withdrawal phase, subjects will take their final dose of double-blind IMP. The subject will return to the clinic for the final trial visit at the double-blind randomized withdrawal phase Week 12 visit. If the subject terminates early from the trial, the end-of-treatment visit procedures should be completed. For subjects who discontinue early, attempts should be made to complete ALL evaluations, particularly efficacy assessments (YGTSS, CGI, etc.), for the Week 12/ET visit prior to the administration of any new psychotropic medications. However, if the subject receives a new psychotropic medication prior to ET procedures, no efficacy assessments should be done. Any prohibited medications started before the end of the trial assessments should be documented as a protocol deviation in the source notes.

The following procedures are to be completed:

1) Current psychotropic therapy will be recorded.
2) The YGTSS and CGI-TS (both the severity and improvement scales) will be performed to assess symptoms associated with TD.
3) Completion of the C-SSRS (children's version).
4) The SAS, BARS, and AIMS will be administered. Benztropine (up to 4 mg/day) is not to be administered 12 hours prior to rating scales. Benzodiazepines (up to

3 mg/day lorazepam equivalents) are not to be administered 4 hours prior to rating scales.

5) A complete physical examination will be performed.
6) Height, body weight, and waist circumference will be measured.
7) Vital sign measurements (systolic and diastolic blood pressure and heart rate) will be recorded. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been sitting for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes.
8) A standard 12-lead ECG will be performed at rest after the subject has been lying down for approximately 5 minutes.
9) Fasting blood samples will be collected for clinical laboratory tests (hematology and serum chemistry, including TSH, glycosylated hemoglobin, and prolactin levels; prolactin samples to remain blinded). If the observed TSH level is outside the normal range, a test of T3 and T4 levels will be performed.
10) Urine will be collected for urinalysis and may be collected for a urine screen(s) for drugs of abuse (can be conducted at any time during the trial at the investigator's discretion).
11) A urine pregnancy test will be done on all FOCBP.
12) For all FOCBP and sexually active males, documentation of birth control methods will be completed.
13) AEs and concomitant medications will be recorded.
14) Drug accountability will be assessed.

3.7.1.9 Post-treatment Follow-up Period

All subjects (completers and subjects who receive at least 1 dose of IMP and discontinue the trial for any reason) will be followed up for safety reasons 30 days (+ 3 days) after the last trial visit. Follow-up will consist of telephone contact to assess any AEs experienced since the last trial visit and information on ongoing AEs and serious TEAEs and recording of concomitant medications, including current psychotropic therapy.

3.7.2 Efficacy Assessments

3.7.2.1 Yale Global Tic Severity Scale

The YGTSS[1] is a semi-structured clinical interview designed to measure current tic severity. This scale consists of a tic inventory, with 5 separate rating scales to rate the severity of symptoms, and an impairment ranking. Ratings are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics, each including number, frequency, intensity, complexity, and interference. Summation of these scores (ie, 0-50)

provides a TTS that will be the primary outcome measure. The YGTSS ranking of impairment, with a maximum of 50 points, is based on the impact of the tic disorder on areas of self-esteem, family life, social acceptance, and school scores. This is a fully validated scale in adults and has become a standard instrument for the evaluation of the severity of TD in children.

3.7.2.2 Clinical Global Impression Scale for Tourette's Syndrome

The severity of illness and efficacy of IMP for each subject will be rated using the CGI-TS scale.[14] To assess CGI-TS severity, the rater or investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" However, the evaluation of illness will be limited to manifestations of TD only. Response choices include: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.

The rater or investigator will rate the subject's total improvement whether or not it is due to drug treatment. All responses will be compared to the subject's condition at baseline (Day 1). Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up labs, if needed). Reports from the central laboratory should be filed with the source documents for each subject. The central laboratory will provide laboratory results to the sponsor electronically.

Samples for serum chemistry, hematology, and urinalysis will be obtained at the visits designated in Table 3.7-1 and Table 3.7-2. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Subjects should be fasting for a minimum of 8 hours prior to any blood draws for all laboratory assessments. If nonfasting blood samples are obtained initially for determining

eligibility for the trial, a fasting blood sample should be drawn at or prior to the baseline visit (prior to the first dose of open-label drug). Microsampling procedures may be used for obtaining blood samples for clinical laboratory analysis in order to minimize the amount of blood drawn from subjects. The laboratory tests to be evaluated in this trial are listed in Table 3.7.3.2-1.

A urine pregnancy test will be performed at screening on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started. Subjects with a positive result at screening will be excluded from the trial. In addition, urine and/or serum pregnancy tests can be performed at any point during the trial for female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started, if pregnancy is suspected. Any positive urine pregnancy test result will be confirmed by a serum pregnancy test. Treated subjects with a positive urine and serum pregnancy test must discontinue treatment, be withdrawn from the trial, and an immediately reportable event (IRE) form should be completed.

Any value outside the normal range will be flagged for the attention of the investigator who must indicate whether or not a flagged value is of clinical significance. If one or more values are questionable, the test(s) may be repeated. If the result of any test (or repeat test, if done) is indicated as clinically significant in the samples taken during the screening period, the subject will NOT be enrolled into the trial without the permission of the medical monitor. In addition, follow-up unscheduled laboratory tests should be performed for clinically significant abnormalities. Unscheduled laboratory tests may be repeated at any time at the discretion of the investigator for appropriate medical care.

Subjects will be excluded from the trial if they have any other abnormal laboratory test result at screening that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results. The following laboratory test results are exclusionary:

1) Platelets ≤ 75,000/mm^3
2) Hemoglobin ≤ 9 g/dL
3) Neutrophils, absolute ≤ 1000/mm^3
4) Aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) as defined by the central laboratory
5) Alanine aminotransferase (ALT) > 3 × ULN as defined by the central laboratory
6) Creatinine ≥ 2 mg/dL

Appendix 2 is included to assist investigators in their assessments of results that may be of potential clinical relevance, depending on the subject's medical history and clinical presentation.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology: Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count with differential	Serum Chemistry: Alkaline phosphatase ALT AST Total bilirubin Blood urea nitrogen Calcium Chloride Cholesterol (total, low-density lipoprotein, and high-density lipoprotein) Creatinine Creatinine phosphokinase Gamma glutamyl transferase Glucose Glycosylated hemoglobin Lactate dehydrogenase Phosphorus, inorganic Potassium Total protein Sodium Triglycerides Uric acid
Urinalysis: Blood Glucose Ketones Microscopic exam (performed only if any part of the urinalysis is not negative) pH Protein Specific gravity	Additional Tests: Prolactinb Serum pregnancy, for confirmation of positive urine tests TSH[a] Urine drug (including alcohol) screen Urine pregnancy (FOCBP)

[a]If the observed TSH level is outside of the normal range, tests of triiodthyronine (T3) and thyroxine (T4) levels will be assessed.

[b]The blinded prolactin results will be reviewed by the designated unblinded medical monitor.

3.7.3.3 Physical Examination and Vital Signs

3.7.3.3.1 Physical Examination

A complete physical examination at the visits designated in Table 3.7-1 and Table 3.7-2. The principal investigator or his/her appointed designee is primarily responsible for performing the physical examination. If the appointed designee is to perform the physical examination, he/she must be permitted by local regulations and his/her name must be

included on the US FDA Form 1572. Whenever possible, the same individual should perform all physical examinations. Any condition present at the post-treatment physical examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion. A complete physical examination is an integral part of study safety assessments and includes a urogenital assessment. A urogenital assessment should be performed on all trial subjects according to local medical standards as applied to other body systems. For the purposes of this trial, at a minimum, a screening urogenital exam is required, which could have been performed up to one calendar year prior to the date of the ICF being signed, or can be performed during the screening period. The urogenital examination may be performed by the subject's primary care provider or pediatrician as long as the source records are obtained and the findings documented. Post-baseline, medically relevant questions about the urogenital body system must be asked of the subject at all protocol-required physical exams, with answers documented accordingly in the source. The extent and scope of any part of the physical examination is to be left to the discretion of the investigator as deemed appropriate for each subject.

3.7.3.3.2 Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure and heart rate and will be performed at all in-clinic visits. If a remote visit is converted to an in-clinic visit, vital signs will be recorded. Vital signs will not be collected for remote visits that are not converted to occur in-clinic.

3.7.3.3.3 Body Weight, Height, and Waist Circumference

Height will be measured with a stadiometer, measuring stick, or tape at the visits designated in Table 3.7-1 and Table 3.7-2. Body weight will be measured at the visits designated in Table 3.7-1 and Table 3.7-2. Waist circumference will be measured with a measuring tape at the visits designated in Table 3.7-1 and Table 3.7-2. The following guidelines will aid in the standardization of these measurements:

- The same scale should be used to weigh a given subject each time.
- Scales should be calibrated and reliable; scales should be at zero just prior to each subject's weigh-in session.
- A subject should void prior to being weighed and be minimally clothed (ie, no shoes or heavy overgarments).
- Weight and waist circumference should be recorded before a subject's meal and at approximately the same time at each visit.

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- The waist circumference measurement will be accomplished by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should assure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.[15]

Utilizing the programing, the BMI (kg/m^2) will be calculated from the height and the weight at the current (or closest preceding) visit using one of the following formulae, as appropriate: Weight (kg) ÷ (Height [m])^2 or Weight (lb) ÷ (Height [in])^2 x 703.

3.7.3.4 Electrocardiogram Assessments

A standard 12-lead ECG will be recorded at the visits designated in Table 3.7-1 and Table 3.7-2. It will be done at rest, with the subject lying down for approximately 5 minutes before the ECG is obtained. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis. The ECG will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator or qualified designee will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant.

Based on the QTcF correction, a subject will be excluded from the trial if the correction is ≥ 450 msec (males) or ≥ 470 msec (females). Subjects with clinically significant ECG findings at screening may enter the open-label stabilization phase only after the screening ECG is repeated and determined by the investigator prior to treatment to have no abnormalities that are clinically significant.

3.7.3.5 Other Safety Assessments

3.7.3.5.1 Extrapyramidal Symptoms

3.7.3.5.1.1 Simpson-Angus Scale

The SAS[16] consists of a list of 10 symptoms of parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of 1 representing absence of symptoms, and a score of 5 representing a severe condition. The SAS Total Score is the sum of the scores for all 10 items.

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3.7.3.5.1.2 Abnormal Involuntary Movement Scale

The AIMS[14] assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (eg, in the waiting room), and the investigator will also make global judgments on the subject's dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness/severe distress). For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes 2 yes/no questions that address the subject's dental status.

The AIMS Movement Rating Score is defined as the sum of items 1 through 7 (ie, items 1 through 4, facial and oral movements; items 5 through 6, extremity movements; and item 7, trunk movements).

3.7.3.5.1.3 Barnes Akathisia Rating Scale

The BARS[17] consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subject distress due to akathisia, and global evaluation of akathisia. The first 3 items will be rated on a 4-point scale, with a score of 0 representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with 0 representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, subjects will be observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (eg, while engaged in neutral conversation or engaged in activity on the ward) may also be rated. Subjective phenomena are to be elicited by direct questioning.

The BARS Global Score is from the global clinical assessment of akathisia from the panel BARS in the eSource.

3.7.3.5.2 Suicidality

Suicidality will be monitored throughout the trial using the C-SSRS (children's version) at every clinic visit. The C-SSRS scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicide events and suicidal ideation and a postbaseline/"Since Last Visit" evaluation that focuses on suicidality since the last trial visit. The baseline C-SSRS form will be completed at the screening visit. The "Since Last Visit" C-SSRS form will be completed at all subsequent visits. If a subject's C-SSRS results indicate active suicidal ideation and a plan/intent, then the results should be

discussed with the medical monitor, when the situation allows it, and the subject may be discontinued from the trial at the discretion of the investigator. Appropriate medical interventions and measures should be undertaken in such cases by the investigator.

3.7.3.5.3 Children's Yale-Brown Obsessive Compulsive Scale

The CY-BOCS[18] is a semi-structured interview used with children and adolescents ages 6 to 17 years to rate the severity and type of symptoms in subjects with OCD. In general, the items depend on the subject's report; however, the final rating is based on the clinical judgment of the interviewer, and should include additional information supplied by others. The characteristics of obsessions and compulsions are rated for the week prior to the interview. The total CY-BOCS score is the sum of items 1 through 10 (excluding lb and 6b); whereas, the obsession and compulsion subtotals are the sums of items 1 through 5 (excluding lb) and 10 (excluding 6b; respectively).

3.7.4 Prior and Concomitant Medications

The investigator will record all medications and therapies taken by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) on the eSource. The investigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) on the eSource.

3.7.5 End of Trial

The end of trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment follow-up eSource page for the last subject completing or withdrawing from the trial.

3.7.6 Interim Analysis Review Committee

This trial will utilize an independent Interim Analysis Review Committee (IARC). The IARC will be responsible for reviewing efficacy data during the IA and will make trial recommendations (Section 7.4.4). The details of the IARC structure and its roles and responsibilities will be documented in an IARC charter.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, IRBs/IECs, and regulatory authorities in accordance with regulatory requirements. One IA is planned (Section 7.4.4) so that the trial can be terminated if the null hypothesis on the comparison between aripiprazole full dose and placebo is rejected at the IA time point.

3.8.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and GCP. The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Interruption

In this approximately year-long trial, it is expected that subjects may have one or more treatment interruptions during the open-label stabilization phase or double-blind randomized withdrawal phase. If a subject's IMP treatment must be interrupted for medical or surgical reasons; liver test abnormalities; use of a prohibited concomitant medication; or other reasons (eg, hospital admission for an invasive procedure, a major medical condition, surgery; dental work, or a temporary situation that prevents subject compliance with the IMP administration schedule), the subject's IMP should be resumed as early as the situation allows (see Section 3.8.3.4). If > 3 doses of IMP are missed in a row, a discussion should occur with the medical monitor to determine if the subject should be discontinued from the trial as a result of the treatment interruption.

3.8.3.2 Treatment Discontinuation

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.5.

3.8.3.3 Documenting Reasons for Treatment Interruption/Discontinuation

A subject may temporarily interrupt or discontinue IMP for a number of reasons including those listed below:

- Reasons related to an AE:
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAE
    - Other potentially IMP-related safety concerns or AEs
- Death
- Reasons unrelated to medical condition (provide detail and review AE history with subject)
- Withdrawal of informed consent (complete written withdrawal of consent form)
- Lost to follow-up
- Pregnancy (see Section 5.5)
- Termination of all or part of the trial by the sponsor
- Tolerability issues requiring down-titration of IMP after the Week 8 visit
- Subject meets the criteria for relapse (ie, a loss of ≥ 50% of the improvement experienced during the open-label stabilization phase (ie, improvement at the last assessment of YGTSS before randomization) on the YGTSS TTS)

If the subject temporarily interrupts or discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 3.8.3.1 and/or Section 3.8.3.2 must be followed.

3.8.3.4 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely

withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up (these methods of follow-up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol-specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to interrupt or discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.1 and Section 3.8.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.8.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be given instructions to meet and discuss with the subject their options of continuing in

the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF/IAF), but who is not randomized or assigned trial treatment.

For the purposes of this trial, treatment begins with the first dose of IMP in the open-label stabilization phase. If a subject fails to qualify for the trial during screening, he/she is permitted to be rescreened at a later date. However, a new ICF/IAF must be signed prior to reinitiating screening procedures. Subjects are permitted to be rescreened only once. Rescreened subjects will be assigned a new screening number.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete the Week 12 visit of the double-blind randomized withdrawal phase will be defined as trial completers. Protocol-specified post-treatment follow-up contacts will not qualify as the "last scheduled visit." Subjects who are not completers are defined as those who "discontinued the trial."

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the double-blind randomized withdrawal phase Week 12 visit, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact

the subject via certified mail or an alternative similar method, where appropriate, before assigning a “lost to follow-up” status.

3.12 Subject Compliance

The date of each IMP administration will be recorded in the eSource. Information regarding any missed or inappropriately administered doses will also be documented in the eSource.

Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in < 80% overall compliance at any point in the trial), discontinuation from the trial should be considered. This decision will be documented by the investigator in consultation with the medical monitor.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject’s continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

The subject’s best medical interests should guide the investigator in the management of conditions that are pre-existing or that develop during the trial (intercurrent illness or AEs). All trial personnel should be familiar with the content of the IB[6] for aripiprazole in order to manage the subject’s condition adequately and select appropriate concomitant medications, if needed. The investigator should carefully assess the potential for interaction with aripiprazole before prescribing any concomitant medications.

All psychotropic medications and any medication for the treatment of tics must be discontinued for at least 2 weeks (14 days) prior to the baseline visit, with the exception

of psychostimulant medications such as, but not limited to, Vyvanse, Adderall, Concerta, Metadate CR, Ritalin LA, Focalin, and Focalin XR, prescribed for the treatment of symptoms of ADHD, which are permitted during the trial. The use of psychostimulant medications is only permitted if the subject did not develop and/or have an exacerbation of the tic disorder after the initiation of treatment with the psychostimulant. The dose of any psychostimulant must have been stable for at least 4 weeks prior to screening. All SSRIs/SNRIs must be discontinued at least 4 weeks (28 days) prior to the baseline visit. In addition, long-acting (depot) neuroleptics must be discontinued for at least 1 full cycle (2 weeks to 1 month, depending on the drug) plus 2 weeks prior to the baseline visit. Other nutritional or dietary supplement and nonprescription herbal preparation for TD (eg, cannabinoids, N-acetylcysteine, omega-3 fatty acids, kava extracts, GABA supplements) are not permitted within 7 days prior to baseline and for the duration of the trial.

Clonidine, guanfacine, guanabenz, atomoxetine, and carbamazepine are prohibited during the trial and must be discontinued for at least 2 weeks prior to the baseline visit. Subjects must have discontinued aripiprazole treatment at least 30 days prior to the screening visit.

The use of cytochrome P450 (CYP)3A4 or CYP2D6 inhibitors and CYP3A4 inducers is not permitted during the trial, as they may affect the PK of aripiprazole. Examples of inhibitors include, but are not limited to amiodarone, celecoxib, chlorpheniramine, cimetidine, clarithromycin, clemastine, diltiazem, erythromycin, itraconazole, ketoconazole, methadone, nefazodone, pyrilamine, quinidine, rifampin, terbinafine, tripelennamine, verapamil and human immunodeficiency virus protease inhibitors (eg, amprenavir, indinavir, nelfinavir, ritonavir and saquinavir). Examples of inducers include, but are not limited to, carbamazepine, dexamethasone, phenobarbital, phenytoin, and nonnucleoside reverse transcriptase inhibitors (eg, efavirenz and nevirapine). The medical monitor should be consulted for any questions regarding the potential for PK interactions with concomitant medications used by subjects during the trial.

Other guidelines for use of concomitant medications during the trial include the following:

- Treatment of extrapyramidal symptoms: Benztropine (up to 4 mg/day) is not to be administered 12 hours prior to rating scales or benzodiazepines (up to 3 mg/day lorazepam equivalents) are not to be administered 4 hours prior to rating scales.
- Treatment of allergy symptoms: Nonsedating antihistamines are permitted.

- Treatment of cold/flu symptoms: Medications containing ingredients that have CNS effects should be limited to short-term use and discontinued as soon as the symptom(s) resolve.
- Treatment of gastroesophageal reflux disease: The use of cimetidine is prohibited. All other medications for the treatment of gastroesophageal reflux disease are permitted.
- Treatment of hypertension: Medications that are CYP3A4 or CYP2D6 inducers or inhibitors (eg, verapamil) are prohibited.
- Treatment of diabetes: No additional guidelines.
- Treatment of infection: No additional guidelines.

4.2 Other Restrictions

4.2.1 Restricted Therapies and Precautions

If there is a need for cognitive-behavioral therapy (CBT) for TD during the trial period, the subject will be excluded from trial participation. No CBT for TD will be allowed during the duration of the trial. CBT for other nonexclusionary disorders must remain consistent throughout the trial.

4.2.2 Nontherapy Precautions and Restrictions

4.2.2.1 Precautions

Subjects should not undergo any elective medical procedure without prior consultation with the investigator. An elective procedure (minor surgery, dental surgery, orthopedic surgery, etc.) that might require hospitalization or anesthesia should be deferred until after the trial whenever clinically appropriate.

4.2.2.2 Restrictions

Subjects will be instructed to refrain from drinking alcoholic beverages or using illicit drugs during participation in the trial. The investigator may request a urine drug screen or a blood alcohol test at any time during the trial if there is a suspicion of illicit drug or alcohol use.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal

relationship with this treatment. AEs would not include information recorded as medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP-related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.4).

- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eSource page if there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eSource. The intensity of an adverse experience is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must

be recorded on the source documents and eSource documentation provided by the sponsor. Serious AE collection is to begin after a subject has signed the ICF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator or site personnel become aware of any SAE, serious hepatotoxicity, or confirmed pregnancy, by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eSource.)

Subjects experiencing SAEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥ 3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE on the eCRF.

5.5 Pregnancy

For purposes of this pediatric trial, FOCBP are considered all female subjects ≥ 12 years of age and all female subjects < 12 years of age, if menstruation has started.

For FOCBP and for males who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (eg, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Two of the following precautions must be used:

vasectomy, tubal ligation, vaginal diaphragm with spermicide, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit. Abstinence will be permitted, if it is documented at every trial visit.

Before enrolling FOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all FOCBP. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject and the subject's legally acceptable representative (eg, guardian) must sign an ICF/IAF stating that the above-mentioned risk factors and the consequences were discussed with them.

A urine pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening on all female subjects ≥12 years of age and all female subjects < 12 years of age, if menstruation has started. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial

discontinuation may be considered for life-threatening conditions only after consultations with the Clinical Safety and Pharmacovigilance department (see the cover page of this protocol for contact information).

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

The investigator is encouraged to contact the sponsor/contract research organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergency situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.7 Follow-up of Adverse Events

For this trial, information on all AEs will be followed for up 30 (+ 3) days after the last dose of IMP has been administered.

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eSource with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eSource. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

This trial requires that subjects be actively monitored for SAEs up to 30 (+ 3) days after the last dose of IMP is administered.

Serious AEs and nonserious IREs that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eSource page. If updated information (eg, resolved status) on SAE or IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eSource, according to the appropriate reporting procedures. The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up or has died.

5.7.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring after Last Scheduled Contact

Any new SAEs reported to the investigator which occur **after the last scheduled contact** and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs or IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs or IREs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

6 Pharmacokinetic Analysis

No PK analysis is planned.

7 Statistical Analysis

7.1 Sample Size

The planned sample size for the double-blind randomized withdrawal phase is 114 subjects (ie, 38 subjects per treatment group). Assuming the proportion of randomized subjects experiencing relapse during the double-blind randomized withdrawal phase will be 65% in the placebo group and 34% in each of the 2 aripiprazole dose groups, 114 subjects will provide approximately 80% power to detect a hazard ratio of 0.4 for release (either aripiprazole dose group versus placebo) at the alpha level of 0.05 (2-sided). Under the above assumptions, a total of 51 relapse events are expected to be observed during the randomization phase. However, subject enrollment will stop when 51 relapse events have accrued or 114 subjects have been randomized, whichever occurs earlier.

The sample size will allow one IA at approximately 70% of events accrual time point. The O'Brian-Fleming boundaries were used for sample size calculation of the interim analysis so that the interim analysis will be conducted when 36 relapse events occur.[19] The 2-sides alpha levels for the IA is 0.016, and the alpha left for the final analysis will be 0.045.

In order to randomize 114 subjects, approximately 228 subjects will need to enter the open-label stabilization phase of the trial, assuming that the stabilization rate is 50%.

7.2 Datasets for Analysis

The following analysis datasets are defined for this trial:

- Open-label Safety Sample: The Open-label Safety Sample includes all subjects that are administered at least one dose of IMP during the open-label stabilization phase.
- Intent to treat (ITT) Sample: All subjects who are randomized and receive at least one dose of randomized IMP will be included in this dataset and analyzed according to the treatment group they are randomized to. The ITT Sample will serve as the primary efficacy dataset for all efficacy endpoints in the double-blind randomized withdrawal phase.

- Randomized Safety Sample: All subjects who receive at least one dose of randomized IMP during the double-blind randomized withdrawal phase will be included and analyzed according to the treatment actually received.

7.3 Handling of Missing Data

The primary endpoint is time from randomization to relapse during the double-blind randomized withdrawal phase. Subjects who complete or discontinue from the randomization phase without relapses will be considered as non-informative censoring in the primary analysis of the primary endpoint. Non-informative censoring means the dropout reason for subject who drops out of the trial without relapse is unrelated to efficacy. However, as the possibility of potential informative censoring in the randomized phase cannot be ruled out, sensitivity analyses of the primary endpoint will be performed under the assumption of informative censoring. Details of such sensitivity analyses will be provided in the statistical analysis plan (SAP).

7.4 Primary and Secondary Endpoint Analyses

7.4.1 Primary Endpoint Analysis

The primary endpoint is time from randomization to relapse during the double-blind randomized withdrawal phase. Subjects who complete or discontinue from the randomization phase without relapses will be considered as censored observations. The primary objective of the trial is to evaluate the long-term efficacy of aripiprazole once-daily treatment in pediatric subjects with TD. This will be accomplished by comparing the long-term efficacy of aripiprazole full-dose and half-dose with that of placebo with regard to time to relapse. Hazard ratio and its 95% confidence interval (CI) will be estimated from the Cox proportional hazard model with treatment as a factor. The p-value from the log rank test will be presented to compare survival (subjects free of relapse) distributions, ie, Kaplan-Meier (KM) curves, between the treatment groups.

Analyses of the primary endpoint will use the data of subjects from the ITT Sample.

The statistical comparison will be performed by the log-rank test comparing each aripiprazole treatment groups with placebo at an overall nominal significance level of 0.05 (two-sided) following a group sequential procedure described as follows. One IA is planned at approximately 70% of events accrual time point using the O'Brian-Fleming boundaries for rejection of the null hypothesis, as detailed in Table 7.4.1-1.

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Table 7.4.1-1 Boundaries for Rejection of Null Hypothesis for Interim and Final Analysis

Analysis	Number of Events	Two-sides Alpha Level[a]
Interim analysis (≈ 70%)	36	0.016
Final analysis (100%)	51	0.045

[a]Obtained using East 6.4 sample size software.

As there are 2 comparisons of the primary endpoint (one for aripiprazole full-dose vs placebo and the other for aripiprazole half-dose vs placebo), Type I error rate will be controlled for the primary endpoint at the alpha level specified in Table 7.4.1-1 using a fixed sequence procedure in the order of the full-dose and then the half-dose comparisons. That is, one must reject the null hypothesis of the comparison of aripiprazole full-dose to placebo at the level of 0.016 for interim analysis and 0.045 for final analysis (two-sided) in order to proceed to test the hypothesis of the comparison of aripiprazole half-dose to placebo at the level of 0.016 for interim analysis and 0.045 for final analysis (two-sided).

As a secondary analysis of the primary endpoint, the proportion of subjects experiencing relapse during the double-blind randomized withdrawal phase will be compared between each of the aripiprazole dose groups to placebo. The proportion of relapsed subjects will be computed as 1 minus the KM estimate of the proportions of subjects free of relapses during the double-blind randomized withdrawal phase. Group difference in the proportion of relapsed subjects will be tested using 2-sided Z test with standard error computed from the Greenwood formula. Point estimate of the group difference and its 95% CI will also be provided

Sensitivity analyses will be conducted to assess the sensitivity of the primary efficacy analysis results to the potential informative censoring which will be detailed in the SAP.

Subgroup analyses may be conducted for the primary endpoint based on subject baseline YGTSS TTS score, sex, and age if specific subgroups have reasonable sample sizes to permit such analyses.

7.4.2 Secondary Endpoint Analysis

Not applicable.

7.4.3 Exploratory Efficacy Endpoint Analysis

7.4.3.1 Open-label Stabilization Phase

Descriptive statistics will be provided for the scores of each efficacy scale assessed during the open-label stabilization phase and their change from trial baseline for the Open-label Safety Sample. For CGI-TS Improvement score, only its observed value at each visit will be summarized.

7.4.3.2 Double-blind Randomized Withdrawal Phase

Exploratory efficacy endpoints during the double-blind randomized withdrawal phase include:

- Mean change from randomization to last visit (Week 12 for completers and withdrawal visit for discontinued subject) in YGTSS TTS score
- Mean change from randomization to last visit (Week 12 for completers and withdrawal visit for discontinued subject) in Total YGTSS score
- Mean change from randomization to last visit (Week 12 for completers and withdrawal visit for discontinued subject) in CGI-TS Severity score
- CGI-TS Improvement score at last visit (Week 12 for completers and withdrawal visit for discontinued subject)

For the above endpoints except the CGI-TS Improvement score, randomization baseline is defined as the assessment taken at the last visit of the open-label stabilization phase prior to the first dose of the randomized IMP.

Variables in the form of change from randomization baseline will be analyzed using mixed model repeated measures (MMRM) under the assumption of missing at random (MAR). The time variable is scheduled visits, which will be treated as a categorical repeated factor. The MMRM model will include terms of treatment, visit, and treatment by visit interactions as fixed categorical effects, baseline as well as baseline by visit interactions as covariates, and a single unstructured covariance matrix assumed for all treatment arms in the model. Restricted maximum likelihood estimates of the treatment difference, their 2-sided 95% CIs and p-values (using Kenward-Roger degrees of freedom) from the MMRM inference will be provided.

The change from randomization baseline to Week 12 of the double-blind randomized withdrawal phase in the above variables will also be analyzed using analysis of covariance (ANCOVA) with missing data being imputed by last observation carried

forward. The ANCOVA model will include treatment as a factor and baseline value as a covariate.

To evaluate the sensitivity of the results to missing data that are potentially missing not at random (MNAR), sensitivity analyses will be conducted with multiple imputations for missing data under the assumption of MNAR, which will be detailed in the SAP.

CGI-TS Improvement score from postbaseline visits will be analyzed in a similar fashion to those change from baseline variables except that there will not be adjustment for baseline value in the analyses of CGI-TS Improvement score.

7.4.4 Interim Analysis

One IA is planned for the assessment of efficacy. The analysis will be performed following a group sequential approach at approximately 70% of events accrual time point and will include all randomized subjects. Subjects who withdraw early from the trial, or who are still in the trial at the end of trial without relapse, will be considered as censored observations. The O'Brian-Fleming boundaries will be used for the IA so that the IA will be conducted when 36 impending relapse events are available. The 2-sided alpha level for the IA is 0.016 and the alpha left for the final analysis will be 0.045 as specified in Table 7.4.1-1. Additionally, a 95% CI for the hazard ratio (either aripiprazole or placebo) will be provided using the Cox proportional hazard model with term of treatment in the model.

If the null hypothesis on comparison between aripiprazole full dose and placebo is rejected at the IA time point, the trial will be terminated. An IA plan will be developed to document the details of the stopping rules, data flow and other logistical considerations relating to the IA.

7.5 Analysis of Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by descriptive statistics including tabulations of mean, median, range, and SD for continuous variables, and tabulations of frequency distributions for categorical variables. These summary statistics will be provided for the Open-label Safety Sample as well as by treatment groups for the ITT Sample.

7.6 Safety Analysis

7.6.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

7.6.1.1 Open-label Stabilization Phase

The incidence of the following events during the open-label stabilization phase will be summarized for the Open-label Safety Sample:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

7.6.1.2 Double-blind Randomized Withdrawal Phase

The incidence of the following events during randomized withdrawal phase will be summarized for the Randomized Safety Sample:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

7.6.2 Clinical Laboratory Data

The incidence of potentially clinically relevant values from clinical laboratory tests will be provided for the open-label stabilization phase and by treatment group for the randomized withdrawal phase with the safety samples appropriate to each phase. In addition, change from baseline in clinical laboratory values will be descriptively

summarized by visit for the Open-label Safety Sample and also by treatment group for the Randomized Safety Sample.

7.6.3 Physical Examination, Vital Signs, Body Weight, and Waist Circumference Data

The incidence of potentially clinically relevant vital sign abnormalities and body weight change will be reported for the open-label stabilization phase and by treatment group for the double-blind randomized withdrawal phase with the safety samples appropriate to each phase. Vital sign parameters, body weight, and waist circumference will also be evaluated by their changes from trial baseline for the Open-label Safety Sample and by change from randomization baseline for each treatment group for the Randomized Safety Sample. The BMI values will be calculated based on height and weight measurements and its results will be summarized by change from baseline similarly to body weight. Physical examination data will be listed.

7.6.4 Electrocardiogram Data

ECG parameters will be evaluated by tabulating the incidence of their clinically relevant changes and by summarizing their changes from the appropriate baseline. Results will be summarized for the open-label stabilization phase and by treatment group for the randomized withdrawal phase with the safety samples appropriate to each phase.

For the analysis of QT and QTc data from 3 consecutive complexes (representing 3 consecutive heart beats) will be measured to determine average values. The following QT corrections will be used:

1) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: QTcF = QT/(RR)0.33
2) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: QTcN = QT/(RR)0.37

7.6.5 Other Safety Data

7.6.5.1 Extrapyramidal Symptoms

Extrapyramidal Symptom scales including SAS, AIMS, and BARS scores will be evaluated by descriptively summarizing their changes from appropriate baseline for the Open-label Safety Sample and by treatment group for the Randomized Safety Sample. Results will be presented by visit.

7.6.5.2 Suicidality

The incidence of suicidality, suicidal behavior and suicidal ideation will be calculated from the potential suicide events recorded on the C-SSRS (children's version) for the single-blind stabilization phase and double-blind randomized withdrawal phase with the safety samples appropriate to each phase.

8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the Aripiprazole IB.[6]

8.1 Packaging and Labeling

Trial medication will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The IR tablet is an immediate-release oral formulation in 4 dose strengths (ie, 2.0, 5.0, 10.0, and 15.0 mg/tablet). Matching placebo tablets will be used in the double-blind randomized withdrawal phase.

The IMP will be labeled to clearly disclose the subject ID, compound ID, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements and other information required by local regulatory authorities.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither the investigators nor any designees may provide IMP to any subject not participating in this protocol. The IMP will be stored according to the storage conditions indicated on the clinical label(s).

The clinical site staff will maintain a temperature log in the drug storage area recording the temperature at least once each working day. Temperature excursions, outside of the specific conditions for the IMP (as noted on the label), will be immediately reported to the sponsor.

8.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational, active control, or placebo) received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMP, and partially-used IMP must be returned to the sponsor or a designated agent, or destroyed at the trial sites. The IMP may only be destroyed by the trial site(s) [if applicable], if approved by the sponsor and if the IMP destruction meets all local regulations.

All IMP returned to the sponsor must be accompanied by appropriate documentation and be identified by protocol number with trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor will facilitate the return or destruction [if applicable] of used IMP containers, unused IMP, and partially-used IMP.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all product quality complaints (PQCs) identified through any means from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or

telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Online – Send information required for reporting purposes (listed below) to [redacted]
- Phone - Rocky Mountain Call Center at [redacted]

Identification of a PQC by the subject should be reported to the site investigator, who should then follow one of the reporting mechanisms above.

8.5.2 Information Required for Reporting Purposes

- Description of compliant
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

It must be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress

notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

Source document and source data will be captured electronically in this trial, and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected into a system that is fully validated. Changes to the data will be captured by an automatic audit trail.

The trial site will be given a tablet to directly record subject data and clinical observations on electronic forms. Designated trial site staff will not be given access to the system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol-required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application - rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified by the trial clinical research associate, and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Another exception will be safety laboratory data, where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source record will take place, however on-site monitoring inspections will continue to take place in order to review data entry source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

9.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a

sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of eSource with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and using screens in eSource, the investigator, sub-investigator and their staff will take measures to ensure adequate

care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject numbers in eSource. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB/IEC. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB/IEC, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

15 References

1 Leckman JF, Zhang H, Vitale A, Lahnin F, Lynch K, Bondi C, et al. Course of tic severity in Tourette Syndrome: The first two decades. Pediatrics. 1998:102(Pt 1):14 9.

2 Cutler D, Murphy T, Gilmour J, Heyman I. The quality of life of young people with Tourette syndrome. Child Care Health Dev. 2009;35:496-504.

3 Golder T. Tourette Syndrome: Information for school nurses. J Sch Nurs. 2010 Feb:26(1):11-7.

4 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.

5 Wong DF, Brasic JR, Singer HS, Schretlen DJ, Kuwabara H, Zhou Y, et al. Mechanisms of dopaminergic and serotonergic neurotransmission in Tourette syndrome: Clues from an in vivo neurochemistry study with PET. Neuropsychopharmacology. 2008;33:1139-51.

6 Aripiprazole Investigator Brochure, Edition 21, 25 Aug 2017.

7 Yoo HK, Joung YS, Lee JS, Song DH, Lee YS, Kim JW, et al. 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.

8 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.

9 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.

10 Lyon GJ, Samar S, Jummani R, Hirsch S, Spirgel A, Goldman R, et al. Aripiprazole in children and adolescents with Tourette's disorder: an open-label safety and tolerability study. J Child Adolesc Psychopharmacol. 2009 Dec;19(6):623 33.

11 Ghanizadeh A. Systemic review of aripiprazole for the treatment of children and adolescents with tic disorders. Neurosciences. 2012 Jul;17(3):200-204.

12 Approved Abilify (aripiprazole) United States prescribing information, Dec 2014; Otsuka America Pharmaceutical, Inc, Rockville, MD.

13 International Conference on Harmonisation (ICH) [homepage on the Internet]. E6: Good Clinical Practice: Consolidated Guideline [finalized 1996 May, corrected 1996 Jun 1996; cited 2014 Dec 5].

14 Guy W. ECDEU Assessment Manual for Psychopharmacology - Revised (DHEW Publication No. ADM 76-338). Rockville, MD, US Department of Health, Education, and Welfare, 1976:218-22.

[15] The Practical Guide: identification, evaluation, and treatment of overweight and obesity in adults. Developed by National Institutes of Health National Heart, Lung and Blood Institute. North American Association for the Study of Obesity. NIH Publication.

[16] Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand. 1970;212:S11-S19.

[17] Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-6.

[18] Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK, et al. Children's Yale-Brown Obsessive Compulsive Scale: Reliability and validity. J Am Acad Child Adolesc Psychiatry. 1997;36:844-52.

[19] O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35(3):549-56.

Protocol 31-14-204

Appendix 1 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate[b]	> 120 bpm < 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic Blood Pressure[b]	> 180 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic Blood Pressure[b]	> 105 mmHg < 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Weight	-	≥ 7% increase ≥ 7% decrease

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

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Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry[a]	
AST (SGOT)	≥ 3 x ULN
ALT (SGPT)	≥ 3 × ULN
Alkaline phosphatase	≥ 3 × ULN
LDH	≥ 3 × ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric Acid	
Male	≥ 10.5 mg/dL
Female	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
CPK	≥ 3 × ULN
Prolactin	> ULN
Hematology[a]	
Hematocrit	≤ 30 % and decrease of ≥ 3 percentage points from baseline
Hemoglobin	
Male	≤ 11.5 g/dL
Female	≤ 9.5 g/dL
White blood count	≤ 2,800 mm^3 or ≥ 16,000 mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 1.5 THOUS/μL
Platelet count	≤ 75,000/ mm^3
Urinalysis[a]	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Hb1Ac	≥ 7%
Potassium	≤ 3.0 mEq/L or ≥ 5.5 mEq/L
Sodium	≤ 120 mEq/L or ≥ 160 mEq/L
Phosphorous, inorganic	≤ 1.0 mg/dL
Magnesium, serum	≤ 0.7 mEq/L or ≥ 5.0 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose, Fasting, serum	≥ 115 mg/dL
Total Cholesterol, Fasting	≥ 240 mg/dL
LDL Cholesterol, Fasting	≥ 160 mg/dL
HDL Cholesterol, Fasting	≤ 30 mg/dL
Triglycerides, Fasting	
Male	≥ 160 mg/dL
Female	≥ 120 mg/dL

[a]As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

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Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 0.20 second	increase of ≥ 0.05 second
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 0.12 second	increase of ≥ 0.02 second
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post trial entry
ST/TMorphological		
Myocardial Ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
	QTc	
Increase in QTc	≥ 450 msec (males) ≥ 470 msec (females)	≥ 10% increase

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c] No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d] No current diagnosis of left bundle-branch block or right bundle-branch block.

Protocol 31-14-204

Appendix 4 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue Date: 30 Apr 2018

PURPOSE:

The purpose of amending the Protocol 31-14-204, issued 08 Jan 2016, was to:

- Add a Week 10 visit to the double-blind phase.
- Allow for remote visits (ie, telemedicine) for selected trial visits.
- Decrease the number of SAS, AIMS, BARS assessments and vital signs measurements.
- Add waist circumference.
- Specify that the C-SSRS is the children's version.
- Add the option of microsampling for clinical laboratory tests.
- Add language for eSource and ePlatform.
- Add an IA.
- Revise language regarding sample size calculation and primary endpoint analysis.
- Clarify inclusion/exclusion criteria.
- Delete OPDC contact information in the appendices.
- Delete sample assessment scales in the appendices.
- Update the protocol to conform to the Otsuka template and style guide.
- Correct minor typographical errors.

BACKGROUND:

Changes to Protocol 31-14-204 were made to improve clarity and to update the protocol per feedback received from the FDA.

Protocol 31-14-204

MODIFICATIONS TO PROTOCOL:

Description of Change	Rationale for Change	Sections Affected by Change
Update of background information	Updated to include information from current Investigator's Brochure (Edition 21).	Section 1.3 Known and Potential Risks and Benefits
Addition of a Week 10 visit during the double-blind phase	Per FDA recommendation.	Protocol Synopsis Section 3.1 Type/Design of Trial Section 3.7. Trial Procedures
Addition of the option of telemedicine at select visits	To potentially improve subject participation by minimizing clinic visits.	Protocol Synopsis Section 3.1 Type/Design of Trial Section 3.7. Trial Procedures
Decrease the number of SAS, AIMS, BARS assessments and vital signs measurements	To limit specific assessments to face-to-face visits.	Protocol Synopsis Section 3.1 Type/Design of Trial Section 3.7. Trial Procedures
Add waist circumference	To add waist circumference whenever body weight is measured.	Protocol Synopsis Section 3.5.2 Safety Endpoint(s) Section 3.7. Trial Procedures Section 7.6.3 Physical Examination, Vital Signs, and Body Weight
Specification that the C-SSRS is the children's version	To specify that the children's version of the C-SSRS will be used, as it is appropriate for this subject population.	Protocol Synopsis Section 3.7. Trial Procedures Section 7.6.5.2 Suicidality
Addition of eSource and ePlatform language	To update language to include eSource and ePlatform technology.	Section 3.4.1 Informed Consent Section 9.2 Data Collection
Revision of sample size calculation	To allow one IA at approximately 70% of events accrual time point.	Protocol Synopsis Section 7.1 Sample Size
Addition of an IA	To include one IA in the protocol.	Protocol Synopsis Section 3.7.6 Interim Analysis Review Committee Section 3.8 Stopping Rules, Withdrawal Criteria, and Procedures 7.4.4 Interim Analysis Review Committee
Revision of primary endpoint analysis	To include additional details about primary endpoint analysis.	Section 7.4.1 Primary Endpoint Analysis
Clarification of inclusion/ exclusion criteria	To clarify inclusion criterion regarding consent/assent, and exclusion criteria regarding substance abuse, herbal medications, and previous clinical trial experience.	Protocol Synopsis Section 3.4 Eligibility Criteria

Protocol 31-14-204

Description of Change	Rationale for Change	Sections Affected by Change
Deletion of OPDC contact information from the appendices	To eliminate the need to modify the protocol due to changes in OPDC personnel.	Appendix 1
Deletion of sample assessment scales in the appendices	It is no longer the Otsuka convention to include sample scales in protocol appendices.	Appendices 5 to 11
Revisions to adhere to the current Otsuka protocol template	To adhere to the current Otsuka protocol template.	Section 3.4.1 Informed Consent/Informed Assent Section 3.7.4 Prior and Concomitant Medications Section 5.4 Potential Serious Hepatotoxicity Section 5.7 Follow-up of Adverse Events Section 3.9 Screen Failures Section 8.4 Returns and Destruction
Correction of minor typographical errors	To adhere to Otsuka standards and style guide.	Throughout protocol

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

A complete redline version of this amendment showing all changes from the previous version will be produced and will be available upon final approval of this amendment.

Protocol 31-14-204

Amendment Number: 2

Issue Date: 20 Jun 2018

PURPOSE:

The purpose of amending the Protocol 31-14-204, Amendment 1, issued 30 Apr 2018, was to:

- Add the EudraCT number.
- Increase the number of proposed sites.
- Specify that randomization will be stratified by region and body weight.
- Clarify exclusion criterion #17.
- Remove the option for the screening visit to be conducted remotely.
- Remove the option for remote visits during the open-label stabilization phase after the Week 12 visit.
- Clarify dose titration and specify when and how dose adjustments are permitted.
- Add language regarding relapse.
- Specify conditions for the measurement of blood pressure.
- Remove triplicate ECGs so that only one ECG is done.
- Add details regarding C-SSRS results.
- Add missing clinical laboratory assessments.
- Correct minor typographical errors and add clarifications to text.

BACKGROUND:

Changes to Protocol 31-14-204 were made to improve clarity and consistency of the document.

Protocol 31-14-204

MODIFICATIONS TO PROTOCOL:

Description of Change	Rationale for Change	Sections Affected by Change
Addition of EudraCT number	Per regulatory requirements	Title Page Protocol Synopsis
Increase in the number of proposed sites	To increase the number of potential sites to 70 sites.	Protocol Synopsis Section 3.1 Type/Design of Trial
Addition of language regarding stratification of randomization	To specify that randomization will be stratified by region and body weight.	Protocol Synopsis Section 3.6.1 Randomization
Clarification of exclusion criterion #17	To specify types of nutritional, dietary, and herbal supplements for TD that are prohibited.	Protocol Synopsis Section 3.4.3 Exclusion Criteria Section 4.1 Prohibited Medications
Removal of option for screening assessments to be done remotely	To ensure consistency of screening assessments.	Protocol Synopsis Section 3.1 Type/Design of Trial Section 3.7. Trial Procedures
Removal of remote visits after Week 12	To ensure appropriate evaluation of subjects and dose titration.	Protocol Synopsis Section 3.1 Type/Design of Trial Section 3.7. Trial Procedures
Provide details regarding dose titration	To ensure appropriate weight-based dosing and titration steps.	Section 3.2 Trial Treatments Section 3.8.3.3 Documenting Reasons for Treatment Interruption/Discontinuation
Addition of language regarding relapse	To state that subjects who meet relapse criteria should be discontinued.	Section 3.1 Type/Design of Trial Section 3.8.3.3 Documenting Reasons for Treatment Interruption/Discontinuation
Specify sitting and standing for blood pressure measurements	To ensure consistency of blood pressure measurements.	Section 3.7. Trial Procedures
Remove triplicate ECGs	To require only one ECG to be done per visit.	Section 3.4.2 Exclusion Criteria Section 3.7. Trial Procedures Section 7.6.4 Electrocardiogram Data
Specify procedures regarding C-SSRS results	To specify that the investigator should discuss C-SSRS results with the medical monitor if they show active suicidal ideation and a plan/intent	Section 3.7.3.5.2 Suicidality
Addition of missing laboratory parameters	To align Table 3.7.3.2-1 with other Otsuka TD protocols.	Table 3.7.3.2-1 Clinical Laboratory Assessments
Correction of minor typographical errors	To adhere to Otsuka standards and style guide.	Throughout protocol

Protocol 31-14-204

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

A complete redline version of this amendment showing all changes from the previous version will be produced and will be available upon final approval of this amendment.

Protocol 31-14-204

Administrative Change Number: 1

Issue Date: 14 Sep 2018

PURPOSE:

The purpose of this administrative change to the Protocol 31-14-204, Amendment 2, issued 20 Jun 2018, was to correct and/or clarify the language related to IRT registration of subjects, collection of vital signs, clinical laboratory tests, ECGs, and administration of the CY-BOCS and K-SADS-PL.

BACKGROUND:

Changes to Protocol 31-14-204 were made to accurately describe the functioning of the ePlatform system, collection of vital signs, clinical laboratory tests, ECGs, and administration of the CY-BOCS and K-SADS-PL.

MODIFICATIONS TO PROTOCOL:

- Deletion of the diagnostic supplement of the K-SADS-PL (Protocol Synopsis, Section 3.4.2: Inclusion Criteria, and Schedule of Assessments [Table 3.7-1 and section 3.7.1.1]).
- Removal of "register subject in IRT" from the Schedule of Assessments (Tables 3.7-1 and 3.7-2 and throughout Section 3.7.1).
- Addition of a footnote to the Schedule of Assessments (Tables 3.7-1 and 3.7-2) to specify that vital signs will be collected at clinic visits only.
- Deletion of insulin from the list of clinical laboratory tests (Table 3.7.3.2-1: Clinical Laboratory Assessments).
- Addition of a statement regarding the central reading of ECGs (Section 3.7.3.4: Electrocardiogram Assessments).
- Clarification regarding the CY-BOCS (Section 3.7.3.5.3: Children's Yale-Brown Obsessive Compulsive Scale).
- Correction of minor formatting issues.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

A complete redline version of this administrative change showing all changes from the previous version of the protocol will be produced and will be available upon final approval of this administrative change.

Protocol 31-14-204

Administrative Change Number: 2

Issue Date: 04 Mar 2019

PURPOSE:

This administrative change will not affect the safety of subjects, the scope of the investigation, or the scientific quality of the trial. The purpose of this administrative change to the Protocol 31-14-204, Amendment 2, Administrative Change 1, issued 14 Sep 2018, was to correct discrepancies between the schedule of assessments and corresponding information regarding collection of vital signs, YGTSS and CGI-TS collection dates, AIMS, BARS, and SAS collection dates, and to clarify language regarding remote visits.

BACKGROUND:

This administrative change to the aripiprazole pediatric Tourette's Disorder Protocol 31-14-204 is to clarify language related to two scales for disease severity and response to therapy, in order to limit risk of protocol deviations and inconsistencies in data collection. The administrative change will resolve language contradictions between the protocol and schedule of assessments facilitating continuity in conduct of this global study across all participating sites.

1) Clarify language regarding vitals assessments, to accommodate administration if clinically indicated. Reconcile any inconsistencies with intent of frequency and schedule of assessments.

2) Resolve inconsistency in protocol relative to schedule of assessments, regarding administration of YGTSS and CGI-TS, which is to be collected at all open-label visits except at Week 3.

3) Resolve contradiction in protocol language as it pertains to administration of AIMS, BARS, and SAS, which should only be conducted at Weeks 1 and 4. The current version (Amendment 2) may be misconstrued, implying administration at Weeks 1 and 2.

4) Currently, Weeks 6 and 10 in the open-label phase and Weeks 3, 6, and 10 in the double-blind phase are listed as visits that can occur by telephone, web, in-clinic, or other acceptable means of contact. The YGTSS is a required assessment on open-label visits Week 6 and 10, and double-blind visits Weeks 3, 6, and 10 which can occur by

telephone, web, in-clinic, or other acceptable means of contact. YGTSS requires visualization of the subject and thus a clarification of this requirement for this scale will be added.

MODIFICATIONS TO PROTOCOL:

- Definition of cycle length for long-acting (depot) neuroleptics added in Section 3.1, Section 3.7.1.1, and Section 4.1.
- Inclusion of C-SSRS added to occur at Week 3 in Schedule of Assessments (Table 3.7-1) and Section 3.7.1.5.
- Inclusion of vital signs at visits 3, 6, 10, 14 and 18 to the Schedule of Assessments (Table 3.7-1).
- Inclusion of vital signs visits at Weeks 3, 6, and 10 to the Schedule of Assessments (Table 3.7-2).
- Revision of footnotes in Schedule of Assessments (Tables 3.7-1 and 3.7-2), Section 3.7.1.4, Section 3.7.1.5, and Section 3.7.1.7 revised to add that if a remote visit is converted to an in-clinic visit, vital signs will be recorded. Vital signs will not be collected for remote visits that are not converted to occur in-clinic.
- Section 3.7.1.4 revised to include Weeks 14 (± 3 days) and 18 (± 3 days) for the procedures of vital signs, IMP dispensing, and drug accountability to occur.
- Section 3.7.1.4. procedures for psychotropic therapy, YGTSS and CGI-TS, documentation of birth control methods, and stability assessments revised to include "at all open-label visits EXCEPT for Week 3".
- Section 3.7.1.5 orthostatic assessment instructions added.
- Section 3.7.1.6.1 randomization procedures updated to clarify subjects should be dispensed IMP and administered the first dose while in the clinical "unless evening dose is preferred".
- The SAS, BARS, and AIMS administer dates corrected in Section 3.7.1.7 to match the Schedule of Assessments and be performed at Week 1 (± 2 days).
- "with direct patient visualization (except for open-label Week 3 which does not require direct patient visualization)," added to the text surrounding telephone visits for Section 3.1 Trial Design, Section 3.7.1 Trial Procedures, footnote under Schedule of Assessments (Table 3.7-1), and Section 3.7.1.4. Footnote under Schedule of Assessments (Table 3.7-2) and Section 3.7.1.4 added "with direct patient visualization".
- Correction of minor wording and formatting issues.

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ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

A complete redline version of this administrative change showing all changes from the previous version of the protocol will be produced and will be available upon final approval of this administrative change.

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Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, OPC-14597, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where OPC-14597 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB- or IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB/IEC approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and sub-investigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

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Document Number: 0000000000

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Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
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