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**
NCT Number:	NCT03661983
Document Date:	SAP Version 1: 06 July 2020

Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Aripiprazole (OPC-14597)

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

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

Statistical Analysis Plan

Phase 3b/4
Version 1.0
Date: Jul 6, 2020

Protocol Version 5.0: 04Mar2019

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1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy and safety data of Trial 31-14-204. This SAP is prepared based on the original protocol and the subsequent protocol amendments.

2 Trial Objectives

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 Tourette's Disorder (TD). 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 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, 6 to 17 years of age, are 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 occurs 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 occur via telephone, web, in-clinic, or other acceptable means of contact. The trial schematic is presented in Figure 3.1-1.

3.1.1 Pretreatment Phase

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.

3.1.2 Open-label Stabilization Phase

The open-label stabilization phase starts with the baseline visit (Day 1). The visits 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. Doses are 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.

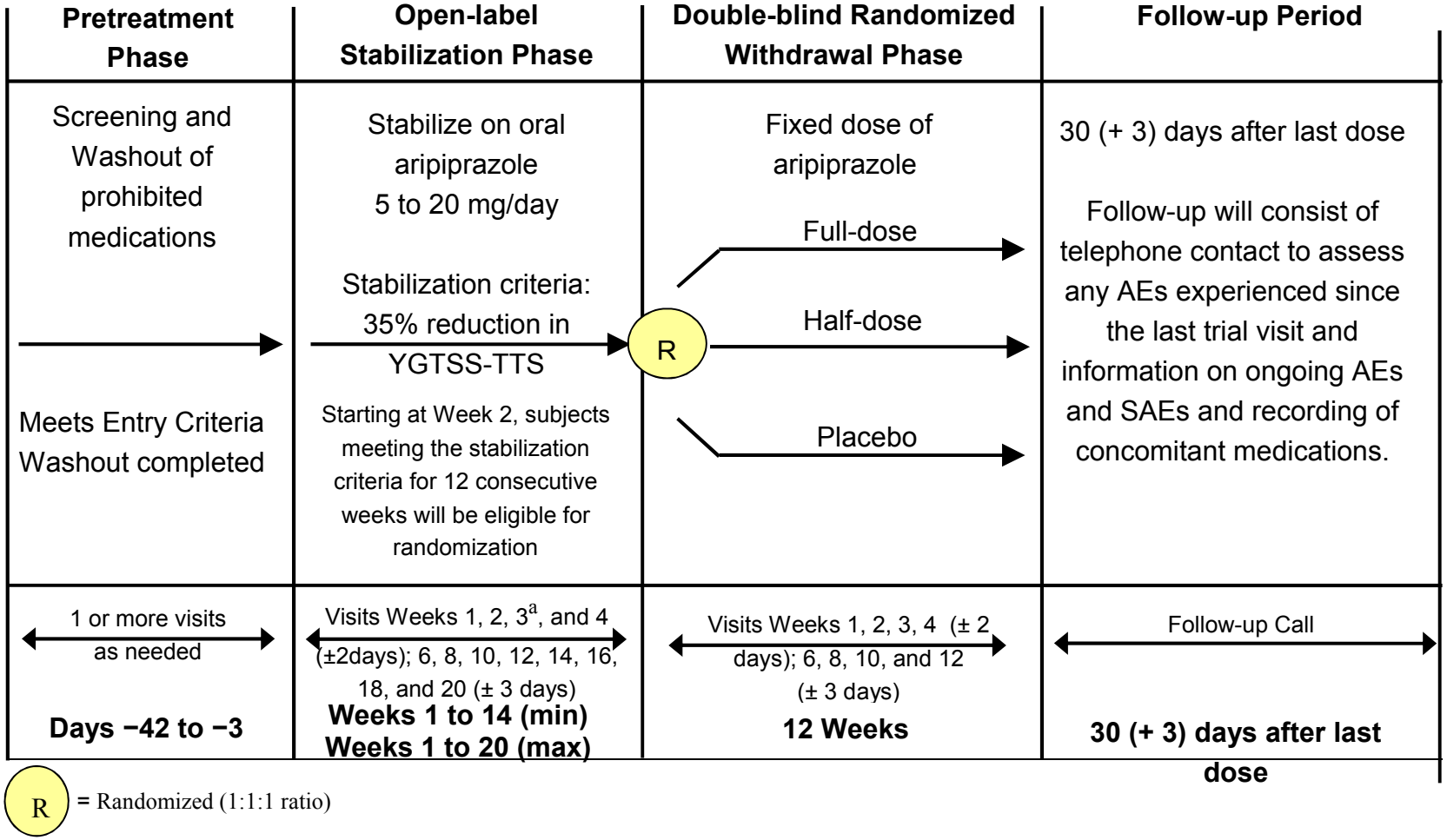
Starting at Week 2, subjects meeting the stabilization criteria (≥ 35% improvement [decrease] of Yale Global Tic Severity Scale Total Tic Score [YGTSS TTS]) who demonstrate a continued response as described (≥ 35% improvement [decrease] of YGTSS TTS) for 12 consecutive weeks, inclusive; with no more than 1 excursion of response criteria 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 are permitted at the end of the 12th consecutive week of stabilization (i.e., the randomization visit). At Week 8, subjects are discontinued if they no longer can achieve 12 weeks of response in the open-label stabilization phase (e.g., the subject has not achieved a response).

3.1.3 Double-blind Randomized Withdrawal Phase

Subjects entering the double-blind randomized withdrawal phase are randomized in 1:1:1 ratio to the half-dose arm, full-dose arm, or placebo arm. Doses in the aripiprazole arms are based on the subject's stabilized dose during the open-label stabilization phase. Subjects 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 are collected. Subjects are 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 (i.e., improvement at the last assessment of YGTSS before randomization) on the YGTSS TTS. If subjects meet relapse criteria, they should be discontinued and treated according to the schedule of assessments.

3.1.4 Safety Follow-up Period

There is 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.



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

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

Several dose strengths of an aripiprazole immediate release tablet formulation are used in this trial: 2.0 mg, 5.0 mg, 10.0 mg, 15.0 mg. Matching placebo tablets are used in the double-blind randomized withdrawal phase entering the double-blind randomized withdrawal phase. Once-daily oral aripiprazole is 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 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 are 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

All enrolled 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 (i.e., 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 is 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 are allowed 1 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 experience 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 (i.e., at least 4 days) prior to being titrated to 20.0 mg.

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

3.2.2 Double-blind Randomized Withdrawal Phase

Subjects meeting the stabilization criteria are 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 are determined using the body weight measurement from the open-label stabilization phase baseline. See Table 3.2.2-1 for the dosing schedule.

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

All subjects 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.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

The trial population includes 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 70 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 are given a unique 5-digit subject screening identification number preceded by an S (SXXXXX).

3.4 Trial Visit Window

Trial Week is derived by mapping trial day into corresponding trial week windows as specified in Table 3.4-1. Trial Day is derived as: Trial Day=Date of assessment - Date of IMP dosing in the corresponding phase + 1. If there are multiple observations within the same time interval, only the last observation within that time interval is used for the summary tables. The trial week window mapping rules are applicable to all data that are reported by trial week unless those data are reported by scheduled visit.

Table 3.4-1 Trial Days and Trial Week Windows

Trial Week	Number of Trial Days in Each Phase	
	Open-label Stabilization Phase	Double-blind Randomized Withdrawal Phase
1	1~10	1~10
2	11~20	11~17
3	N/A	18~24
4	21~34	25~34
6	35-48	35-48
8	49~62	49~62
10	63~76	63~76
12	77~90	77~97
14	91~104	N/A
16	105~118	N/A
18	119~132	N/A
20	133~146	N/A

Note: N/A=not applicable.

4 Sample Size

The planned sample size for the double-blind randomized withdrawal phase is 114 subjects (i.e., 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.

The sample size is estimated to allow 1 Interim Analysis 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. 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%.

5 Statistical Analysis Datasets

5.1 Analysis Datasets

The following analysis datasets are defined for the report of this trial:

- Enrolled Sample: The enrolled sample includes all subjects who entered the open-label stabilization phase.
- Open-label Efficacy Sample: The Open-label Efficacy Sample includes all subjects that are administered at least 1 dose of IMP and have at least 1 assessment of efficacy endpoints during the open-label stabilization phase.
- Open-label Safety Sample: The Open-label Safety Sample includes all subjects that are administered at least 1 dose of IMP during the open-label stabilization phase.
- Randomized Sample: The Randomized Sample included all subjects who are randomized into the double-blind randomized withdrawal phase no matter if he/she takes IMP in randomization phase.
- Intent to treat (ITT) Sample: All subjects who are randomized and receive at least 1 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 1 dose of randomized IMP during the double-blind randomized withdrawal phase will be included and analyzed according to the treatment received.

5.2 Definition of Baseline and Last Visit

Baseline for Open-label Stabilization Phase is defined as the last visit with available data prior to the first dose in Open-label Stabilization Phase. Last visit in Open-label Stabilization Phase is defined as the last visit with available data prior to randomization, or on/before early termination in the Open-label Stabilization Phase.

Baseline for Double-blind Randomized Withdrawal Phase is defined as the last visit of the Open-label Stabilization Phase prior to the first dose of double-blind IMP in Double-blind Randomized Withdrawal Phase. Last visit in Double-blind Randomized Withdrawal Phase is defined as the last visit with available data at the completion or on/before early termination for the randomized subjects.

5.3 Handling of Missing Data

The observed case (OC) dataset consist of the actual observations recorded at each visit and will be used to present summaries per trial week for efficacy endpoints. No missing data will be imputed.

6 Primary and Secondary Endpoints

6.1 Primary Efficacy Endpoint

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

6.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are not applicable.

6.3 Exploratory Efficacy Endpoints

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

- Change from randomization to last visit in YGTSS TTS score;
- Change from randomization to last visit in Total YGTSS score;
- Change from randomization to last visit in CGI-TS Severity score;
- CGI-TS Improvement score at last visit.

6.4 Safety Endpoints

Safety endpoints include the following:

- Adverse events (AEs)
- Laboratory tests (hematology, serum chemistry 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

7 Summary of Trial Data

The following data will be summarized for enrolled sample and randomized sample if applicable.

7.1 Subject Disposition

Disposition of subjects including screened subjects and/or randomized subjects will be reported by phase and treatment group. Subject enrollment will be summarized by age group (6-12 years old and 13-17 years old), region, country and center. Durations of subjects staying in each phase will be summarized by treatment group. Reasons for discontinuations will be tabulated by phase and treatment group. Subjects who complete the Week 12 visit of the double-blind randomized withdrawal phase are defined as trial completers.

7.2 Demographic and Baseline Characteristics

Demographic characteristics including age, weight, height, BMI, waist circumference, sex, race, ethnicity, region (North American, rest of world), categories for weight (< 50kg, >=50 kg) and age (7-12 years old and 12-17 years old) will be summarized using descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable) and reported by treatment group.

Disease characteristics at baseline and psychiatric history (including efficacy assessments and age of initial diagnosis for TD) will be presented by phase and treatment group. In

calculating age of first diagnosis for TD, if both month and day are missing, June 1 is used. If only day is missing, date of 1 is used. If only month is missing, month June is used.

7.3 Treatment Compliance

For each subject, compliance of IMP will be calculated separately for each phase. compliance for open-label stabilization phase will be calculated from number of days exposed to oral aripiprazole divided by number of days in open-label stabilization phase. Compliance will be derived from the total number of oral tablets taken divided by the expected total number of tablets expectedly taken in double-blind randomized withdrawal phase. The expected number of IMP tablets in double-blind randomized withdrawal phase is 2 tablets per day. Proportion of randomized sample reaching at least 50%, 60%, 70%, 80% and 90% compliance for aripiprazole oral tablets in each phase will be tabulated by treatment group in randomized withdrawal phase. Compliance of IMP will also be summarized for enrolled sample in open-label stabilization phase.

7.4 Prior and Concomitant Medications

Proportion of subjects taking concomitant medications will be tabulated by drug classification using the WHO drug dictionary (WHODRUG Global B3, March 2020 or later) by treatment group for randomized sample prior to start of open-label stabilization phase, during open-label stabilization phase, during/after double-blind randomized withdrawal phase, respectively. The concomitant medications tabulation will be summarized for enrolled sample regarding those periods also.

7.5 Protocol Deviations

Protocol deviations will be summarized by classification of deviations, phase and treatment group in addition to by center. Listing will be provided describing the deviations for each enrolled subject with indication of relevance to COVID-19 outbreak if applicable.

8 Efficacy Analyses

8.1 Primary Efficacy Endpoint

8.1.1 Primary Endpoint Analysis

The primary endpoint is time from randomization to 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 (i.e., improvement at the last

assessment of YGTSS before randomization) on the YGTSS TTS. Since this trial has terminated early due to withdrawal of postmarking commitment (PMC), only relapse rate will be provided by treatment group for ITT sample.

8.2 Exploratory Efficacy Endpoints

8.2.1 Exploratory Efficacy Endpoints Analysis

Descriptive statistics for the following efficacy endpoints will be provided by trail week and last visit for open-label efficacy sample in open-label stabilization phase and ITT sample in double-blinded randomized withdrawal phase, respectively.

- Change from randomization to last visit in YGTSS TTS score;
- Change from randomization to last visit in Total YGTSS score;
- Change from randomization to last visit in CGI-TS Severity score;
- CGI-TS Improvement score at last visit.

The YGTSS 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 (i.e., 0-50) provides a YGTSS-TTS score. 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. Total YGTSS score is sum of YGTSS-TTS score and impairment score with range of 0 to 100.

The severity of illness and efficacy of IMP for each subject will be rated using the CGI-TS scale. 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 it is due to drug treatment. All responses will be compared to the subject's condition at baseline. 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.

9 Safety Analyses

Safety analysis will be conducted based on open-label and randomized safety samples, which are defined in Section 5.1. Safety variables to be analyzed include AEs, clinical laboratory tests, physical examinations, vital signs, ECGs, suicidality via the C-SSRS (children's version). In general, safety data will be summarized using descriptive

statistics (where applicable) by treatment group for open-label safety sample in open-label stabilization phase and randomized safety sample in double-blinded randomized withdrawal phase, respectively.

9.1 Extent of Exposure

Exposure to IMP for randomized safety sample in open-label stabilization phase and double-blinded randomized withdrawal phase will be summarized in percentage of subjects' exposure and average daily dose for each week by treatment group in randomized phase. Exposure to IMP for open-label safety sample during open-label stabilization phase will be also provided in percentage of subjects' exposure and average daily dose by week.

9.2 Adverse Events

All adverse events (AEs) are coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term (Version 23.0 or later). A treatment-emergent AE (TEAE) is defined as an AE which starts after start of trial medication (Aripiprazole IM depot/Oral tablets), or an AE continues from baseline of the specific phase and becomes serious, trial drug-related or results in death, discontinuation, interruption or reduction of study medication during this phase. The incidences of the following treatment-emergent adverse events (TEAEs) will be summarized by treatment group for the safety samples:

- TEAEs by severity
- Potentially drug related TEAEs
- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs
- Death
- Non- Serious TEAEs

Deaths, SAEs, and AEs leading to discontinuation from the trial will be listed for the safety samples.

9.3 Clinical Laboratory Data

Clinical laboratory tests include serum chemistry analysis, hematology analysis, urinalyses and other lab analysis. The potentially clinically relevant laboratory test abnormalities are listed by subject and by test for the safety samples. Criteria for identifying laboratory values of the potential clinical relevance are provided in Appendix 1. Subjects with AST or ALT > 3 times upper limit of normal (ULN) value and total

bilirubin > 2 times ULN values if pre-treatment value is <= ULN value, or with AST or ALT > 3 times pre-treatment value and total bilirubin > 2 times pre-treatment value if pre-treatment value is > ULN value, are listed by phase. The incidences of potentially clinically relevant laboratory tests abnormalities based on the observation from the scheduled and the unscheduled post-baseline visits will be tabulated for the safety samples. Descriptive statistics for the clinical laboratory measurements and changes from baseline at each scheduled trial week and last visit will be presented for the safety samples.

If laboratory tests assessments are repeated for the same visit, the last repeated values are used for summary tables. This is accomplished by sorting patient data by visit date and visit time (if applicable) within the same visit identification. If the lab data are recorded as ranges (i.e., including < or > limit of quantification), these data are not included in the calculations for changes from baseline but included in the calculations for incidences.

9.4 Vital Sign Data

Vital signs include body temperature, heart rate, systolic blood pressure and diastolic blood pressure in supine and sitting position. In addition, body weight and waist circumference are measured. Potentially clinically relevant vital sign abnormalities will be listed by subject. Criteria for identifying vital signs of the potential clinical relevance are provided in Appendix 2. Incidences of clinically relevant vital signs abnormalities based on the observation from the scheduled and unscheduled post-baseline visits will be tabulated safety samples. In addition to weight, BMI and waist circumference, vitals sign parameters at each trial week, and change from baseline at the post-baseline trial weeks will be summarized using descriptive statistics for the safety samples in the corresponding phases.

If vital sign assessments are repeated for the same trial week, the last repeat values will be used for production of mean change from baseline. This is accomplished by sorting patient data by visit date and visit time (if applicable) within the same visit identification.

9.5 Electrocardiogram Data

All ECG analyses are made using observed data. Baseline is defined as average of ECG measurements at baseline visit as specified in Section 5.2. Last visit for each phase is defined as average of ECG measurements at last visit as specified in Section 5.2. Missing ECG data will not be imputed. For the calculation of QT correction by heart rate, QTc is missing only if all three consecutive beats are unreadable. If there is at least 1 beat available in the lead, the data are included in the analysis. For each ECG, QT and RR

intervals from three consecutive complexes (representing three consecutive heart beats) are measured manually. The QT correction is performed on beat-to-beat basis. The mean of ratios (beat-to-beat) is calculated by $(QT_c1 + QT_c2 + QT_c3)/3$ using each QT-RR pair: (QT1, RR1), (QT2, RR2) and (QT3, RR3). The corrected QT intervals for QT_cB, QT_cF, and QT_cN are defined as follows:

- QT_cB is the length of the QT interval corrected for heart rate by Bazett's formula: $QT_cB = QT / (RR)^{1/2}$.
- QT_cF is the length of the QT interval corrected for heart rate by Fredericia's formula: $QT_cF = QT / (RR)^{1/3}$.
- QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN = QT/(RR)^{0.37}$.

Potentially clinically relevant ECG abnormalities will be listed by subject. Criteria for identifying ECG measurements of the potentially clinically relevance are provided in Appendix 3. The incidences of abnormal ECGs of potential clinical relevance based on the observation at the scheduled and the unscheduled post-baseline visits will be tabulated the safety samples. Descriptive statistics of change from baseline in ECG intervals of PR, QRS, RR, QT, QTcB, QTcF, and QTcN will be presented at each scheduled trial week and last visit for the safety samples.

In summarizing the incidence of abnormalities, a patient must have had an evaluation that meets abnormality criteria by the end of trial phase. Incidence rate is calculated as the number of patients having at least 1 abnormality within the corresponding study phase divided by the number of patients who are both exposed to study medication and have an on-treatment evaluation within the same study phase.

If ECG assessments are repeated for the same trial week, the last repeat values will be used for production of mean change from baseline. This is accomplished by sorting patient data by visit date and visit time (if applicable) within the same visit identification.

9.6 Other Safety Data

9.6.1 Extrapyramidal Symptoms

EPS rating scales include the Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS) and Abnormal Involuntary Movement Scale (AIMS). The following variables will be analyzed: 1) Change from Baseline in SAS Total Score, 2) Change from Baseline in BARS Global Score, 3) Change from Baseline in AIMS Movement Rating Score (i.e., total of item 1 to 7).

The SAS total score (range 10-50) is the sum of the rating scores for 10 items from the SAS panel in the eCRF. The BARS global score (range 0-5) is derived from the global

clinical assessment of akathisia from the BARS panel in the eCRF. The AIMS movement rating score (range 0-28) is the sum of the rating scores for facial and oral moments (i.e., item 1 - 4), extremity movements (i.e. item 5 - 6), and trunk movements (i.e. item 7) from the AIMS panel in the eCRF. A missing value of any item for SAS and AIMS movements scale could result in a missing SAS total score or AIMS movement rating score.

Changes from baseline in EPS scale scores will be summarized by trial week for the safety samples. EPS rating scale scores will be presented for OC datasets.

9.6.2 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) in the single-blind stabilization phase and double-blind randomized withdrawal phase for the safety samples. Suicidality will be assessed based on C-SSRS data. Data for the Baseline Version of the C-SSRS and Since Last Visit Version of the C-SSRS data will be summarized descriptively and presented in a listing.

The baseline version of C-SSRS is administered at the screening visit and the "Since Last Visit" version is administered at all subsequent visits. Baseline and post-baseline C-SSRS data will be summarized to report the incidence of suicidality, suicidal behavior and suicidal ideation. Suicidality is defined as reporting at least 1 occurrence of any suicidal behavior or suicidal ideation. Suicidal behavior is defined as reporting any type of suicidal behaviors. Suicidal ideation is defined as reporting any type of suicidal ideation.

In addition, C-SSRS data collected post-baseline will also be summarized to report the incidence of completed suicide, emergence of suicidal ideation, emergence of serious suicidal ideation, worsening of suicidal ideation and emergence of suicidal behavior. Any completed suicide is considered as complete suicidality. Emergence of suicidal ideation is defined as having no suicidal ideation at screening and baseline and reporting any type of ideation during treatment. Emergence of serious suicidal ideation is defined as having no suicidal ideation at screening and baseline and reporting any type of suicidal ideation with ideation severity rating of 4 or 5 during treatment. Worsening of suicidal ideation is defined as occurring when the most severe suicidal ideation rating during treatment is more severe than its worst rating at screening and baseline. Emergence of suicidal behavior is defined as having no suicidal behavior at screening and baseline and reporting any type of suicidal behavior during treatment.

10 Pharmacokinetic Analyses

None.

11 Pharmacodynamic Analyses

None.

12 Pharmacogenomic Analyses.

None.

13 Interim Analysis

None.

14 Changes in the Planned Analyses

This trial was terminated due to withdrawal of postmarking commitment, so the interim analysis specified in the protocol was not to be conducted. The descriptive statistics will be provided for all the efficacy endpoints.

Appendix 1 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).

Appendix 2 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).

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
Increase in QTc	QTc ≥ 450 msec (males) QTc ≥ 470 msec (females)	≥ 10% increase ≥ 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.

Appendix 4 Proposed Summary Tables and Data Listings

Proposed Summary Tables:

CT-1.1.1 Subject Disposition by Phase
CT-1.1.2 Subject Disposition in Double-Blind Randomized Withdrawal Phase (Randomized Sample)
CT-1.2.1 Subject Enrollment by Region, Country and Center
CT-1.2.1 Subject Enrollment by Region, Country and Center (Randomized Sample)
CT-1.3.1 Subject Enrollment by Age Group at Enrollment
CT-1.3.2 Subject Enrollment by Age Group at Enrollment (Randomized Sample)
CT-2.1 Reasons for Discontinuation by Phase (Enrolled Sample)
CT-2.2 Reasons for Discontinuation (Randomized Sample)
CT-3.1.1 Demographic Characteristics (Enrolled Sample)
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CT-3.2.1 Baseline Disease Characteristics (Enrolled Sample)
CT-3.2.2 Baseline Disease Characteristics (Randomized Sample)
CT-4.1 Concomitant Medications: Medications Taken by Phase (Open-Label Safety Sample)
CT-4.2.1 Concomitant Medications: Medications Taken Prior to Start of Study Therapy (Randomized Safety Sample)
CT-4.2.2 Concomitant Medications: Medications Taken During Open-Label Stabilization Phase (Randomized Safety Sample)
CT-4.2.3 Concomitant Medications: Medications Taken During Double-Blind Randomized Withdrawal Phase (Randomized Safety Sample)
CT-4.2.4 Concomitant Medications: Medications Taken Post Study Therapy Period (Randomized Safety Sample)
CT-5.1 Descriptive statistics for Relapse Rate (ITT Sample)
CT-5.2.1 Yale Global Tic Severity Scale - Total Tic Score (YGTSS - TTS) - Mean Change from Baseline by Week - OC (Open-Label Efficacy Sample)
CT-5.2.2 Yale Global Tic Severity Scale - Total Tic Score (YGTSS - TTS) - Mean Change from Baseline by Week - OC (ITT Sample)
CT-5.3.1 Total Yale Global Tic Severity Scale Score - Mean Change from Baseline by Week - OC (Open-Label Efficacy Sample)
CT-5.3.2 Total Yale Global Tic Severity Scale Score - Mean Change from Baseline by Week - OC (ITT Sample)
CT-5.4.1 Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) Severity score - Mean Change from Baseline by Week - OC (Open-Label Efficacy Sample)
CT-5.4.2 Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) Severity score - Mean Change from Baseline by Week - OC (ITT Sample)
CT-5.5.1 Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) Improvement Score - Mean by Week - OC (Open-Label Efficacy Sample)
CT-5.5.2 Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) Improvement Score - Mean by Week - OC (ITT Sample)
CT-6.1.1 Simpson-Angus Scale Total Score - Mean Change from Baseline by Week - OC (Randomized Safety Sample)
CT-6.1.2 Barnes Akathisia Rating Scale Global Score - Mean Change from Baseline by Week - OC (Randomized Safety Sample)
CT-6.1.3 AIMS Movement Rating Score - Mean Change from Baseline by Week - OC (Randomized Safety Sample)
CT-6.2.1 Columbia-Suicide Severity Rating Scale (C-SSRS) (children's version) - Suicidality (Randomized Safety Sample)
CT-6.2.2 Columbia-Suicide Severity Rating Scale (C-SSRS) (children's version) by Type (Randomized Safety Sample)
CT-7 Extent of Exposure to Investigational Medicinal Products Double-Blind Randomized Withdrawal Phase (Randomized Safety Sample)
CT-8.1 Adverse Events (All Causalities) (Randomized Safety Sample)

CT-8.2.1 Incidence of Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Randomized Safety Sample)
CT-8.2.2 Incidence of Treatment-Emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Severity (Randomized Safety Sample)
CT-8.2.3 Incidence and Occurrence (Number of Events) of non-Serious Treatment-emergent Adverse by System Organ Class and MedDRA Preferred Term (Randomized Safety Sample)
CT-8.3.1 Incidence and Occurrence (Number of Events) of Potentially Drug-Related Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred (Randomized Safety Sample)
CT-8.3.2 Incidence of Potentially Drug-related Treatment-emergent Adverse Events by System Organ Class and MedDRA Preferred Term and Severity (Randomized Safety Sample)
CT-8.4 Incidence of Deaths Due to Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Randomized Safety Sample)
CT-8.5.1 Incidence and Occurrence (Number of Events) of Serious Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Randomized Safety Sample)
CT-8.5.2 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class and MedDRA Preferred Term and Severity (Randomized Safety Sample)
CT-8.6.1 Incidence of Treatment-Emergent Adverse Events Resulting in Discontinuation from Trial by System Organ Class and MedDRA Preferred Term (Randomized Safety Sample)
CT-8.6.2 Incidence of Treatment-Emergent Adverse Events Resulting in Discontinuation from Trial by System Organ Class, MedDRA Preferred Term and Severity (Randomized Safety Sample)
CT-9.1 Listing of Deaths (Safety Sample)
CT-9.2 Listing of Serious Adverse Events (Safety Sample)
CT-9.3 Listing of Discontinuations of Study Medication Due to Adverse Events(Safety Sample)
CT-10.1.1 Laboratory Test Results for Serum Chemistry - Mean Change from Baseline (Randomized Safety Sample)
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CT-10.1.3 Laboratory Test Results for Urinalysis - Mean Change from Baseline (Randomized Safety Sample)
CT-10.1.4 Laboratory Test Results for Other Clinical Laboratory Tests - Mean Change from Baseline (Randomized Safety Sample)
CT-10.2 Incidence of Laboratory Values of Potential Clinical Relevance (Randomized Safety Sample)
CT-10.3.1 Listing of Laboratory Values of Potentially Clinical Relevance by Subject(Safety Sample)
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CT-10.4 Listing of Potentially Liver Injury Related Laboratory Test Abnormalities by Subject (Safety Sample)
CT-11.1.1 Vital Sign Parameters - Mean Change from Baseline (Randomized Safety Sample)
CT-11.1.2 Mean Change from Baseline in Weight, Height, BMI and Waist Circumference (Randomized Safety Sample)
CT-11.2 Incidence of Vital Signs of Potential Clinical Relevance (Randomized Safety Sample)
CT-11.3.1 Listing of Vital Signs of Potentially Clinical Relevance by Subject(Safety Sample)
CT-11.3.2 Criteria for Potentially Clinically Relevant Vital Sign Abnormalities
CT-12.1 ECG Parameters - Mean Change from Baseline (Randomized Safety Sample)
CT-12.2 Incidence of ECG Measurements of Potential Clinical Relevance (Randomized Safety Sample)
CT-12.3.1 Listing of ECG Measurements of Potentially Clinical Relevance (Safety Sample)
CT-12.3.2 Criteria for ECG Measurements of Potentially Clinical Relevance
CT-13.1.1 Simpson-Angus Scale Total Score - Mean Change from Baseline by Week - OC (Open-Label Safety Sample)
CT-13.1.2 Barnes Akathisia Rating Scale Global Score - Mean Change from Baseline by Week - OC (Open-Label Safety Sample)
CT-13.1.3 AIMS Movement Rating Score - Mean Change from Baseline by Week - OC (Open-Label Safety Sample)
CT-13.2.1 Columbia-Suicide Severity Rating Scale (C-SSRS) (children's version) - Suicidality (Open-Label Safety Sample)

CT-13.2.2 Columbia-Suicide Severity Rating Scale (C-SSRS) (children's version) by Type (Open-Label Safety Sample)
CT-14 Extent of Exposure to Investigational Medicinal Products in Open-Label Stabilization Phase (Open-Label Safety Sample)
CT-15.1 Adverse Events (All Causalities) (Open-Label Safety Sample)
CT-15.2.1 Incidence and Occurrence of Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Open-Label Safety Sample)
CT-15.2.2 Incidence of Treatment-Emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Severity (Open-Label Safety Sample)
CT-15.3.1 Incidence and Occurrence (Number of Events) of Potentially Drug-Related Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred (Open-Label Safety Sample)
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CT-15.6.1 Incidence of Treatment-Emergent Adverse Events Resulting in Discontinuation from Trial by System Organ Class and MedDRA Preferred Term (Open-Label Safety Sample)
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CT-16.1.1 Laboratory Test Results for Serum Chemistry - Mean Change from Baseline (Open-Label Safety Sample)
CT-16.1.2 Laboratory Test Results for Hematology - Mean Change from Baseline (Open-Label Safety Sample)
CT-16.1.3 Laboratory Test Results for Urinalysis - Mean Change from Baseline (Open-Label Safety Sample)
CT-16.1.4 Laboratory Test Results for Other Clinical Laboratory Tests - Mean Change from Baseline (Open-Label Safety Sample)
CT-16.2 Incidence of Laboratory Values of Potential Clinical Relevance (Open-Label Safety Sample)
CT-17.1.1 Vital Sign Parameters - Mean Change from Baseline (Open-Label Safety Sample)
CT-17.1.2 Mean Change from Baseline in Weight, Height, BMI and Waist Circumference (Open-Label Safety Sample)
CT-17.2 Incidence of Vital Signs of Potential Clinical Relevance (Open-Label Safety Sample)
CT-18.1 ECG Parameters - Mean Change from Baseline (Open-Label Safety Sample)
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DREAS-2 Adverse Events for Subjects Who Discontinued from Trial due to Withdrew Consent
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PDEV-3 All Protocol Deviations by Subject
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DEMOG-1 Demographic Characteristics
SMED-1.1 Summary of Trial Medication Compliance in Double-Blind Randomized Withdrawal Phase (Randomized Sample)
SMED-1.2 Trial Medication Compliance in Double-Blind Randomized Withdrawal Phase (Randomized Sample)
SMED-2.1 Summary of Trial Medication Compliance in Open-Label Stabilization Phase (Enrolled Sample)
SMED-2.2 Trial Medication Compliance in Open-Label Stabilization Phase (Enrolled Sample)

EFF-1 Relapse Data
EFF-2.1 Yale Global Tic Severity Scale - Total Tic Score (YGTSS - TTS) and Total Yale Global Tic Severity Scale Score
EFF-2.2 Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) Severity and Improvement Scores
AE-1.1 Adverse Events in Open-Label Stabilization Phase (Enrolled Sample)
AE-1.2 Adverse Events in Double-Blind Randomized Withdrawal Phase (Randomized Sample)
AE-1.3 Adverse Events in Follow-up Period (Enrolled Sample)
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LAB-6 Laboratory Test Results: Urine Pregnancy Test (Enrolled Sample)

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PDATA-2 Randomization List
PDATA-3.1 Subject Disposition
PDATA-3.2 Study Completion Status and Reasons for Discontinuation
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PDATA-16 Barnes Akathisia Rating Scale (BARS)
PDATA-17 Abnormal Involuntary Movement Scale (AIMS)
PDATA-18 Columbia Suicide Severity Rating Scale (C-SSRS)
PDATA-19 Screening Failures
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Document Number: 1000073116

Document Version: 2.0

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[redacted]	Biostatistics Approval	06-Jul-2020 22:25:19