Statistical Analysis Plan for Interventional Studies

Text only

SAP Text Version Number: 3.0
SAP Text Date: (DD-Mmm-YYYY): 6-Dec-2023

Sponsor Name: Emalex Biosciences, Inc.

Protocol Number: EBS-101-TD-301
Protocol Title: A Multicenter, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Safety and Maintenance of Efficacy of Ecopipam in Children, Adolescents and Adults with Tourette's Disorder

Protocol Version and Date: (DD-Mmm-YYYY): **7**.0 (15-Sep-2023)

Syneos Health Project Code: 7038072

Author: [redacted]

Notice of Confidential and Proprietary Information:

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	27-Jun-2023	[redacted]	Final Version 1.0

2.0	5-Oct-2023	[redacted]	Final Version 2.0. Updated to address FDA comments and Protocol amendment V7 **Summary of Changes:** **General:** 1. Updated protocol and SAP version numbers, dates, study personnel 2. Various minor text clarifications including fixing typographical and grammar errors, clarifications of information to be included in tables, clarifications on how missing items within scales will be handled 3. Updated text per protocol version 7.0 changes with regards to: a. timing of PK sample collection; b. enrollment into the OL study EBS-101-TD-391; c. inclusion/exclusion criteria; d. schedule of events; e. exploratory endpoint wording **Specific:** 4. Section 7. Estimands: a. updated population and intercurrent events sections of primary estimand 5. Section 8. General Aspects for Statistical Analysis: a. added definitions for several derived variables, b. clarified visit windows for early term visits 6. Section 10. Efficacy: a. clarified statistical analysis methods for MMRM models, notably covariance structure; b. included all visits in MMRM models of change from baseline; c. changed analysis of Clinical Global Impression of Tourette Syndrome Improvement (CGI-TS-I) and the Caregiver Global Impression of Change (CaGI-C) Baseline to Week 24 endpoints to a non-parametric method 7. Section 13. Interim Analysis: a. corrected conditional power formula and test statistic
3.0	6-Dec-2023	[redacted]	Final Version 3.0.

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
			Updated to address FDA comments and add exploratory endpoints from protocol erroneously overlooked in previous versions **Summary of Changes:** **Specific:** 1. Section 7. Estimands: a. updated intercurrent events section of primary estimand 2. Section 8. General Aspects for Statistical Analysis: a. corrected adult BMI z-score formula 3. Section 10. Efficacy: a. updated methodology for non-converging covariance structure b. added exploratory YGTSS subscales from protocol

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

[redacted]

Name, Title	Signature	Date (DD-Mmm-YYYY)
Lead Biostatistician		

[redacted]

Name, Title	Signature	Date (DD-Mmm-YYYY)
Senior Reviewing Biostatistician		

Emalex Biosciences, Inc. Approval

[redacted]

Name, Title	Signature	Date (DD-Mmm-YYYY)
Sponsor Contact		

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
ADHD	Attention Deficit/Hyperactivity Disorder
ADR	Adverse Drug Reaction
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical classification
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats Per Minute
C&A-GTS-QOL	Child and Adolescent Gilles de la Tourette Syndrome-Quality of Life Scales
CAARS-S:S	Conners' Adult ADHD Ratings Scale- Self Report: Short Version
CAC	Clinical Adjudication Committee
CaGI-C	Caregiver Global Impression of Change
CDC	Centers for Disease Control and Prevention
CDRS-R	Children's Depression Rating Scale-Revised
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-TS-I	Clinical Global Impression Tourette's Syndrome of Improvement
CGI-TS-S	Clinical Global Impression Tourette's Syndrome of Severity
CI	Confidence Interval
cm	Centimeter
COVID-19	SARS-CoV-2 (coronavirus)
CP	Conditional Power
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Toxicity Criteria for Adverse Events

Abbreviation	Description
CTC	Common Toxicity Criteria
CV	Coefficient of Variation
CY-BOCS-II	Children's Yale-Brown Obsessive Compulsive Scale-II
DCI	Diagnostic Confidence Index
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition-Text Revision
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESRS	Extrapyramidal Symptom Rating Scale
ET	Early Termination
F/U	Follow-Up
FCS	Full Conditional Specification
GTS-QOL	Gilles de la Tourette Syndrome-Quality of Life Scales
HAM-A	Hamilton Rating Scale for Anxiety
HbA1c	Hemoglobin A1c
HCG	Human Chorionic Gonadotropin
HDL	High-Density Lipoprotein
HR	Heart Rate
IA	Interim Analysis
IND	Investigative New Drug application
ITT	Intention-to-Treat set
IWRS	Interactive Web Randomization System
kg	Kilogram
LDL	Low-Density Lipoprotein
LS	Least Squares
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Description
mITT	Modified Intention-to-Treat set
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not at Random
N	Number of observations
NCI	National Cancer Institute
OCD	Obsessive-Compulsive Disorder
ODAE	Off Study Drug AE
OLAE	Open-Label AE
PARS	Pediatric Anxiety Rating Scale
PHQ-9	Patient Health Questionnaire – 9
PK	Pharmacokinetics
PKS	Pharmacokinetics set
PP	Per-Protocol set
PUTS	Premonitory Urge for Tics Scale
QTcB	QT interval, Bazett's correction
QTcF	QT interval, Fridericia's correction
R/WD	Randomized-Withdrawal
RWDAE	Randomized-Withdrawal AE
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	International System of Units
SNAP-IV-26	Swanson, Nolan, and Pelham-IV-26 questionnaire
SOC	System Organ Class
SS	Safety Set
TD	Tourette's Disorder
TDAE	Taper Down AE
TEAE	Treatment-Emergent AE

Abbreviation	Description
TS	Tourette's Syndrome
TTS	Total Tic Score
US	United States
VAS	Visual Analog Scale
Y-BOCS-II	Yale – Brown Obsessive Compulsive Scale-II
YGTSS	Yale Global Tic Severity Scale
YGTSS-GS	Yale Global Tic Severity Scale-Global Severity
YGTSS -TTS	Yale Global Tic Severity Scale - Total Tic Score

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all datasets, tables, figures, and listings.

2.2. Timings of Analyses

The primary analysis of safety and efficacy and/or pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study and the database is locked.

An Interim analysis will be conducted in coordination with the Data Safety Monitoring Board (DSMB), meeting to primarily assess safety and conditional power after approximately 70% of relapse events have accrued (34 relapse events). See Section 13 for complete details.

3. Study Objectives

3.1. Primary Objective

The primary objective of this study is to evaluate the maintenance of efficacy of ecopipam tablets in children (≥ 6 and < 12 years of age) and adolescents (≥ 12 and < 18 years of age) with Tourette's Disorder (TD).

3.2. Secondary Objectives

The secondary objectives of this study are to evaluate the safety and tolerability of ecopipam dosed at 1.8 mg/kg/day (2 mg/kg/day ecopipam HCl) in children (≥ 6 and < 12 years of age), adolescents (≥ 12 and < 18 years of age), and adults (≥ 18 years of age) with TD, to evaluate the maintenance of efficacy of ecopipam in adults (≥ 18 years of age), and to characterize the pharmacokinetics (PK) of ecopipam in all subjects.

3.3. Exploratory Objective

To evaluate the population PK/pharmacodynamic (PD) relationships with ecopipam during the open-label Stabilization period of the study and additional exploratory endpoints listed in section 5.3.

4. Study Details/Design

4.1. Brief Description

This is a multicenter study which includes an open-label period followed by double-blind, placebo-controlled, randomized withdrawal period in children (≥ 6 and < 12 years of age), adolescents (≥ 12 and < 18 years of age), and adult subjects (≥ 18 years of age) with TD.

After providing informed consent (adult subjects or caregivers for children/adolescents) and assent (children/adolescents) and following an up to 28-day Screening period, and with agreement by Eligibility Review by the study team, subjects will proceed to the Baseline visit (Day 1).

At the Baseline visit, eligible subjects will be entered into an open-label Stabilization period and start a 4-week Titration phase to achieve a target steady-state dose of 1.8 mg/kg/day ecopipam (2mg/kg/day ecopipam HCl) followed by an 8-week open-label Maintenance phase.

During the open-label Stabilization period, subjects will return to the clinic at Baseline (Day 1) and Weeks 4, 8 and 12. Subjects will have a telephone visit at Week 2 to assess adverse events (AEs) and other safety parameters. Efficacy assessments will be conducted at Weeks 4, 8 and 12. PK samples will be collected at Weeks 4 and 8. A PK assessment may be collected at Week 12 if the Week 8 PK assessment is missed. Safety assessments will be conducted at all visits.

Responders to ecopipam, defined as those with ≥ 25% improvement from Baseline on the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) at both Weeks 8 & 12 during the open-label Stabilization period, will be randomized to ecopipam 1.8 mg/kg/day (2 mg/kg/day ecopipam HCl) or placebo in a 1:1 fashion and enter a double-blind Randomized-Withdrawal (R/WD) period at Week 12. Subjects randomized to placebo will be tapered off ecopipam in a blinded fashion in decrements of 22.4-mg/day (25-mg/day ecopipam HCl).

During the R/WD period, subjects will return to the clinic every week for the first 4 weeks and every 2 weeks thereafter (Weeks 13, 14, 15, 16, 18, 20, 22 and 24) and efficacy and safety assessments will be conducted at each of these visits. Any subject meeting Relapse criteria, defined as the loss of ≥ 50% of the improvement experienced on the YGTSS-TTS from Baseline (Day 1) to the last visit of the open-label Stabilization period Week 12, or initiation of additional medications to treat symptoms of TD, or requirement of hospitalization for worsening symptoms of TD will be withdrawn from blinded study medication (ecopipam or placebo).

An interim analysis (IA) will be conducted by an independent data safety monitoring board (DSMB) after approximately 70% of Relapse events have accrued (34 Relapse events). For details, please refer to section 13.

Non-responders to ecopipam during the open-label Stabilization period at either Week 8 or Week 12, or Responders randomized to ecopipam who complete the R/WD period, or who meet Relapse criteria during the R/WD period, or any subjects who discontinue the study prematurely for any reason will be

tapered off ecopipam in decrements of 22.4-mg/day and will complete the Week 24/Relapse/ET visit. Subjects assigned to placebo will receive placebo taper down medication to preserve the blind.

Follow Up visits will be conducted in the clinic 7 and 14 days after the last dose of study medication. Subjects will also be contacted by telephone 30 days after the last dose of study medication to determine any adverse events, with the exception of subjects who roll into the open-label extension study EBS-101-TD-391 within 30 days of their last study drug.

Subjects who experience Relapse may be treated for their TD with medications recommended by the PI or referred back to their primary physician for treatment after completing Day 7 and 14 follow-up visits.

Responders to ecopipam who complete the R/WD period and who complete the Week 24/Relapse/ET visit and the Day 7 and 14 follow-up visits are eligible to enter into the long-term open-label study EBS-101-TD-391. Subjects who meet the criteria for Relapse and complete the Week 24/Relapse/ET visit and the Day 7 and 14 follow-up visits will have the opportunity to enter the long-term open-label study.

Randomization into the double-blind R/WD period may be closed in anticipation of reaching the target number of Relapse events. Subjects still in the open-label Stabilization period at that point may continue in the study until the Week 12 visit and upon completion of that visit subjects will have the opportunity to enter into the long-term open-label study, EBS-101-TD-391. The Sponsor may elect to re-open randomization as required.

Once the target number of Relapse events is met, all subjects may enter the long-term open-label study EBS-101-TD-391 once the Week 24/Relapse/ET visit and the Day 7 and 14 follow-up visits have been completed.

The study will be considered completed once all subjects have completed the 30-Day telephone Follow Up call or entered the open-label study EBS-101-TD-391.

4.2. Subject Selection

4.2.1. Inclusion Criteria

Subjects eligible for inclusion in this study must fulfill all the criteria listed in section 8.1 of the protocol.

4.2.2. Exclusion Criteria

Subjects will not be eligible if they meet any of the criteria listed in section 8.2 of the protocol.

4.3. Determination of Sample Size

The planned number of Relapse events for the double-blind R/WD Phase is 49 in children and adolescents. This number of events will provide 85% power to detect a difference between treatment groups, assuming a hazard ratio of 0.4 for Relapse and statistical testing at alpha level 0.05 (2-sided). Subject enrollment will stop around the time that 49 Relapse events among children and adolescents are anticipated to have occurred. The number of Relapse events among adults will not determine study completion.

Assuming the proportion of subjects who Relapse in the DB randomization phase is 65% in the placebo group and 34% in the ecopipam group, approximately 98 subjects (49 subjects per group) will be required to achieve this number of Relapse events.

Total Number of Subjects:

Approximately 196 subjects (children and adolescents) will be enrolled into the open-label Stabilization Period in order to randomize 98 subjects age ≥ 6 to < 18 years of age assuming the stabilization Response rate in the open-label Stabilization Period is 50%. In addition, approximately 40 adult subjects are also expected to be enrolled.

4.4. Treatment Assignment and Blinding

Eligible subjects will receive open label ecopipam tablets for up to 12 weeks. Subjects who qualify as Responders to ecopipam in the open-label Stabilization period will be randomized 1:1 to either ecopipam or matching placebo for the R/WD 12- week period. Randomization will be stratified by weight band (≥18 to ≤23 kg, >23 to ≤34 kg, >34 to ≤44 kg, >44 to ≤68 kg, >68 to ≤83 kg, >83 kg).

Throughout the study, subjects, caregivers, and all personnel involved with the conduct and interpretation of the study, including the subject, parents/guardians, investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the Sponsor or Syneos and accessible only to authorized persons (e.g., Safety) until the time of unblinding.

A master list of all treatments and the subject numbers associated with them will be maintained electronically in the Interactive Web Randomization System (IWRS). The process to request a randomization code will be outlined in IWRS user manual. The site will be trained in this process, and it should be used only in an emergency. These codes should only be broken if knowledge of the subject's randomization code will affect his/her medical treatment. If possible, before breaking the blind, the Investigator should consult with the Sponsor to ascertain the necessity of breaking the code. The Investigator is to record the date and time of requesting the code and the reason for breaking the code.

4.5. Administration of Study Medication

During the 4-week titration phase of the open-label Stabilization period, the following ecopipam doses will be administered PO for each of the weight bands (see Table 1):

Table 1: Proposed Dosing Regimen

Weight (kg)	Week 1		Week 2		Week 3		Week 4	
	ecopipam mg/day	ecopipam HCl mg/day	ecopipam mg/day	ecopipam HCl mg/day	ecopipam mg/day	ecopipam HCl mg/day	ecopipam mg/day	ecopipam HCl mg/day
≥18 - ≤23	11.2	12.5	22.4	25	33.6	37.5	33.6	37.5
>23 - ≤34	11.2	12.5	22.4	25	33.6	37.5	44.8	50
>34 - ≤44	11.2	12.5	22.4	25	44.8	50	67.2	75

>44 - ≤68	22.4	25	44.8	50	67.2	75	89.6	100
>68 - ≤83	22.4	25	44.8	50	89.6	100	134.4[1]	150[1]
>83	22.4	25	44.8	50	89.6	100	179.2[2]	200[2]

[1] 134.4 mg ecopipam dose (150 mg ecopipam HCl) given as two tablets containing 67.2 mg ecopipam (75 mg ecopipam HCl) each.

[2] 179.2 mg ecopipam dose (200 mg ecopipam HCl) given as two tablets containing 89.6 mg ecopipam (100 mg ecopipam HCl) each.

Subjects who do not tolerate the dose titration up to the full designated dose for their weight stratum will be discontinued from the study. These subjects will be tapered off their current dose of study drug according to their weight stratum.

During Weeks 4 to 12 of the open-label maintenance phase and for Responders in this period who are randomized to ecopipam for the 12-week R/WD period, the following ecopipam HCl doses will be administered for each of the weight bands:

Those who weigh ≥18 - ≤23 kg will receive 33.6 mg (37.5 mg ecopipam HCl) daily.

Those who weigh >23 - ≤34 will receive 44.8 mg (50 mg ecopipam HCl) daily.

Those who weigh >34 - ≤44 will receive 67.2 mg (75 mg ecopipam HCl) daily.

Those who weigh >44 - ≤68 kg will receive 89.6 mg (100 mg ecopipam HCl) daily.

Those who weigh >68 - ≤83 kg will receive 134.4 mg (150 mg ecopipam HCl) daily.

Those who weigh >83 kg will receive 179.2 mg (200 mg ecopipam HCl) daily.

All doses will be administered PO once daily in the evening without regard to food. Subjects who have changes in weight during the study will not have their doses adjusted for the duration of the study.

Responders who are randomized to placebo for the 12-week R/WD period, will taper off ecopipam in decrements by 22.4 mg/day (25 mg/day ecopipam HCl) until off study drug. For the remainder of the R/WD period, these patients will receive matching placebo tablets. Any subject randomized to placebo who meets Relapse criteria during the R/WD period, or who discontinues the study prematurely due to any reason will receive a taper kit of matching placebo with the same number of tablets as subjects in same weight band receiving blinded ecopipam to preserve the blind. All subjects will be monitored for signs or symptoms of withdrawal, abuse, and dependence.

Non-responders to ecopipam during the Stabilization period, or Responders randomized to ecopipam who complete the R/WD period, or who meet Relapse criteria during the R/WD period, or who discontinue the study prematurely due to any reason will be tapered off ecopipam in decrements of 22.4 mg/day (25 mg/day ecopipam HCl) until off drug. All subjects will be monitored for signs or symptoms of withdrawal, abuse and dependence.

4.6. Study Procedures

After the screening period, subjects will return to the clinic at Baseline and 4, 8 and 12 weeks of the open-label stabilization period. Subjects will have a telephone visit at Week 2 to assess adverse events (AEs) and other safety parameters. Efficacy assessments will be conducted at Weeks 4, 8 and 12. Safety assessments will be conducted at all visits. During the R/WD period, subjects will return to the clinic every week for the first 4 weeks and every 2 weeks thereafter (Weeks 13, 14, 15, 16, 18, 20, 22 and 24) and efficacy and safety assessments will be conducted at each of these visits.

A Follow Up visit will be conducted in the clinic 7 and 14 days after the last dose of study medication. Subjects will also be contacted 30 days after the last dose of study medication to determine any adverse events. At study completion or early termination, subjects will be tapered off study drug as outlined in the protocol. See Table 3 from the protocol for the Schedule of Assessments.

5. Endpoints

5.1. Primary Efficacy Endpoint

- Time from Randomization (Week 12) to Relapse in subjects between the ages of ≥ 6 and <18 years for ecopipam compared to those receiving placebo during the double-blind, R/WD period.

5.2. Secondary Efficacy Endpoint

- Time from Randomization (Week 12) to Relapse in all subjects irrespective of age for ecopipam compared to those receiving placebo during the double-blind, R/WD period.

5.3. Exploratory Endpoints

1. Time from Randomization (Week 12) to a worsening by at least one category of the Global Impression Tourette's Syndrome of Severity (CGI-TS-S) in subjects ≥ 6 and < 18 years for ecopipam compared to those receiving placebo during the double-blind, R/WD period. If there is a strong correlation of this endpoint with Relapse criteria based on the YGTSS-TTS, it may be considered as a secondary endpoint with agreement from Health Authorities.
2. Time from Randomization (Week 12) to a worsening by at least one category of the CGI-TS-S in all subjects for ecopipam compared to those receiving placebo irrespective of age. If there is a strong correlation of this endpoint with Relapse criteria based on the YGTSS-TTS, it may be considered as a secondary endpoint with agreement from Health Authorities.
3. Mean change from Randomization (Week 12) to Week 24 in the YGTSS-TTS for ecopipam compared to placebo.
4. Mean change from Randomization (Week 12) to Week 24 in the CGI-TS-S for ecopipam compared to placebo.
5. Mean change from Randomization (Week 12) to Week 24 in the YGTSS-Global Severity (GS) Score for ecopipam compared to placebo.
6. Mean change from Randomization (Week 12) to Week 24 in the Caregiver Global Impression of Change (CaGI-C) for ecopipam compared to placebo.
7. Time from Randomization (Week 12) to a loss of ≥ 50% of the improvement from Baseline (Day 1) experienced on the YGTSS-TTS at the last visit (Week 12) in the open-label Stabilization period.
8. Mean change from Randomization (Week 12) to Week 24 in the Clinical Global Impression of Tourette Syndrome Improvement (CGI-TS-I) for ecopipam compared to placebo.
9. Mean change from Randomization (Week 12) to Week 24 in the Premonitory Urge for Tics Scale (PUTS) for ecopipam compared to placebo.
10. Mean change from Baseline (Day 1) to Week 24 in Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) score for ecopipam compared to placebo.
11. Mean change from Baseline (Day 1) to Week 24 in Gilles de la Tourette Syndrome–Quality of Life Scale (GTS-QOL) score in adults for ecopipam compared to placebo.

12. Mean change from Baseline (Day 1) to Week 12 in the YGTSS-TTS.
13. Percentage of subjects with a decrease in their YGTSS-TTS by 25% or greater at any time point from Baseline (Day 1) to Week 12.
14. Mean change from Baseline (Day 1) to Week 24 in the YGTSS-TTS for ecopipam compared to placebo.
15. Mean change from Baseline (Day 1) to Week 24 in the YGTSS-GS score for ecopipam compared to placebo.
16. Mean change from Baseline (Day 1) to Week 24 in the Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) for ecopipam compared to placebo.
17. Caregiver Global Impression of Change (CaGI-C) through Week 24 for ecopipam compared to placebo.
18. Mean change from Randomization (Week 12) to Week 24 in the Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) for ecopipam compared to placebo.
19. Clinical Global Impression of Tourette Syndrome Improvement (CGI-TS-I) through Week 24 for ecopipam compared to placebo.
20. Time from Randomization (Week 12) to treatment discontinuation during the double-blind R/WD period for ecopipam compared to placebo.
21. Time from Randomization (Week 12) to loss of ≥ 100% of the improvement experienced on the YGTSS-TTS from Baseline (Day 1) to the last visit (Week 12) in the open-label Stabilization period for ecopipam compared to placebo.
22. To evaluate the population PK/pharmacodynamic (PD) relationships with ecopipam during the open-label Stabilization period of the study.
23. Mean change from Randomization (Week 12) to Week 24 in the YGTSS subscales (Motor, Vocal, and Impairment) for ecopipam compared to placebo.
24. Mean change from Baseline (Day 1) to Week 24 in the YGTSS subscales (Motor, Vocal, and Impairment) for ecopipam compared to placebo.

6. Analysis Sets

6.1. Screened Set

The Screened Set will include all subjects screened. Unless specified otherwise, this set will be used for subject listings and for summaries of subject disposition.

6.2. Safety Set

The Safety Set (SS) will include all enrolled subjects who received at least one dose of study drug. The SS will be used for the analysis of the safety endpoints.

6.3. Modified Intent-to-Treat (Primary Efficacy Analysis Set)

The Modified Intention-to-Treat (mITT) set will include all randomized subjects who received at least one dose of study drug post randomization. The mITT set will be used for the analysis of primary, secondary and exploratory efficacy endpoints. Subjects will be analyzed according to randomized treatment.

6.4. Intention-to-Treat Set

The Intention -to -Treat Set (ITT) will include all randomized subjects. While the mITT will be the primary population for efficacy analysis, regulatory authorities may require or prefer an analysis based on the ITT population. All analyses performed for the mITT population will also be performed for the Intent-to-Treat population. Subjects will be analyzed according to randomized treatment.

6.5. Per Protocol Set

The Per-Protocol (PP) set will include subjects from mITT set who have no major protocol deviations that may adversely impact assessment of efficacy. Before data are released for statistical analysis, a blinded review of all data will be performed by the Sponsor's clinical team to identify protocol deviations that may potentially affect the results. At this time, it will be determined whether subjects and/or data should be excluded from the PP set. The list of subjects or observations to be excluded from the PP set, along with the reason for exclusion, will be finalized prior to database unblinding. Protocol deviations that occur due to COVID-19 related issues or other qualifying events will be categorized separately as applicable.

6.6. Pharmacokinetic Set

The Pharmacokinetic Set (PKS) will include all subjects who received at least one dose of the study drug and have at least one valid PK concentration measured.

PK concentrations will be listed for all subjects in the PK set.

6.7. Protocol Deviations

Protocol deviations will be collected and categorized as shown in the protocol deviation and non-compliance management plan.

7. Estimands

7.1. Primary Efficacy Estimand

The primary estimand is defined as the following:

Treatment: 4-week titration period followed by 8-week maintenance during open label stabilization period and 12 weeks of double blinded withdrawal period with ecopipam HCl doses or matching placebo.

Population: Children and adolescent patients with Tourette's syndrome.

Primary Endpoint: Time from Randomization (Week 12) to Relapse (defined as loss of ≥ 50% of the improvement experienced on the YGTSS-TTS from Baseline (Day 1) to the last visit in the open-label Stabilization period (Week 12), or initiation of additional medications to treat symptoms of TD, or requirement of hospitalization for worsening symptoms of TD) in subjects between the ages of ≥ 6 and <18 years for ecopipam compared to those receiving placebo during the double-blind, R/WD period.

Intercurrent events:

The intercurrent events of initiation of additional medications to treat symptoms of TD and requirement of hospitalization for worsening symptoms of TD are included in the definition of Relapse and are considered a Relapse. The intercurrent event of loss to follow-up will be assumed unrelated to treatment and treated in estimation as censored observations. The intercurrent event of death will be handled as follows: if judged unrelated to blinded treatment or TD, death will be treated in estimation as a censored observation; if death is judged as related to blinded treatment or TD then it will be considered a Relapse. Judgement on whether a death is related to blinded treatment will be made prior to data unblinding. Data from subjects who complete or discontinue from the double-blind R/WD period without Relapse will be considered as censored observations.

Population-level summary: The time from Randomization to Relapse between the ecopipam and placebo treatment groups will be tested using a log rank test in the mITT population after having applied the treatment policy strategy specified above.

The primary efficacy analysis approach is in line with the primary estimand. Potential confounders will be identified and sensitivity and/or supplementary analysis may be used to deal with missing data and assess the robustness of conclusions.

7.2. Secondary Efficacy Estimand

The secondary endpoint is Time from Randomization (Week 12) to Relapse in all subjects irrespective of age for ecopipam compared to those receiving placebo during the double-blind, R/WD period.

This time-to event endpoint related to Relapse will follow the same treatment policy strategy as the primary efficacy endpoint.

8. General Aspects for Statistical Analysis

8.1. General Methods

Study EBS-101-TD-301 is a multicenter global study. Investigative sites in the US are considered conducted under IND 109746 and non-US investigative sites are considered not conducted under IND 109746. Tables, Listings, and Figures will contain combined data from IND and non-IND investigative sites.

All analyses and outputs will be produced using SAS® version 9.4 or later. Unless otherwise specified, efficacy and safety summaries will be presented for each treatment. Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency, and percentages of subjects. Time-to-event variables will be summarized using Kaplan-Meier estimates of the 25th percentile, median and 75th percentile.

All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings. All by-visit summaries will use the nominal visit. Unscheduled visits will not be summarized but will be included in the listings.

8.2. Key Definitions and Derivations

Treatment emergent adverse events (TEAEs) are defined as any adverse events that start or increase in intensity on or after the first dose of treatment on Day 1.

Timing-specific adverse events are defined as any adverse events that occur or increase in intensity during any specifically defined study milestones: open-label stabilization period (OLAE), double-blind R/WD phase (RWDAE), taper down (TDAE) and off study drug (ODAE).

Prior medications are defined as medications entered in the eCRF that either start, or end before the first dose of study medication. Concomitant medications are defined as medication on the eCRF that are taken on or after or are ongoing at the start date of dosing.

Duration of exposure (days) to study drug is defined as (Date of Last Dose – Date of First Dose) +1. If the date of last dose is unknown, then the date of last clinical visit will be used to impute the date of last dose.

Baseline is defined as the last measurement taken before the first dose of ecopipam in the open-label stabilization period.

Change from baseline will be calculated for the post-baseline assessments as post-baseline value – baseline value. Similarly, change from randomization will be calculated for the post-randomization assessments as post-randomization value – randomization value.

Demographics and baseline characteristics will be derived as follows:

Age at Study Day 1 = (Study day 1 visit date - date of birth + 1) / 365.25 and truncated to complete years.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m2) = Weight(kg)/[Height(m)2]

To calculate weight, height and BMI z-scores for children and adolescents, Centers for Disease Control and Prevention (CDC) growth charts will be used (see section 13)

For adults, weight, height and BMI z-scores will be calculated as follows:

(Weight, Height and BMI) z-scores = (Weight, Height and BMI) - mean (Weight, Height and BMI) of all subjects at the baseline visit/ Standard deviation of (Weight, Height and BMI) of all subjects at the baseline visit.

Treatment compliance, as a percentage, will be derived on the eCRF as follows:

Treatment compliance (%) = Actual Tablets Used*100/Expected Tablets Used

Actual Tablets Used is based on Tablets Dispensed minus (Tablets Lost or Discarded + Tablets Returned)

Expected Tablets Used is based on the Number of Days between visits and the Number of Tablets required to achieve assigned dosage based on the subject's baseline weight.

YGTSS scores will be derived without imputing missing values. The scores will be calculated only if all the questions are answered.

- Total Motor Tic Severity Score (range 0-25) = Motor Number + Frequency + Intensity + Complexity + Interference
- Total Vocal Tic Severity Score (range 0-25) = Vocal Number + Frequency + Intensity + Complexity + Interference
- Total Tic Severity Score (range 0-50) = Motor Tic Severity + Vocal Tic Severity
- Total Yale Global Tic Severity Scale Score (range 0-100) = (Total Tic Severity Score + Impairment)

8.3. Missing Data

Partial dates of medications will be imputed solely for the purpose of defining prior/concomitant status for medications. Dates will be defined using the hierarchy of derivations below.

- For missing start day where month and year are present, the start day will be set to the 1st of the month, unless the month and year are the same as the first dose month and year and the 1st of the month is before the first dose date, in which case, the start date will be set to the first dose date.
- For missing start day and month where year is present, the start day and month will be set to

January 1st, unless the year is the same as the first dose year and January 1st is before the first dose date, in which case, the start date will be set to the first dose date.

- For missing end day where month and year are present, the end day will be set to the last day of the month, unless the month and year are the same as the trial termination month and year, in which case, the end date will be set to the trial termination date.

- For missing end day and month, where year is present, the end date will be set to the trial termination date if the years are the same. If the trial termination year is greater than the end year, the end day and month will be set to December 31st.

Partial onset dates for adverse events will be imputed in the same manner described above for partial start dates for the purpose of defining treatment emergent status.

8.4. Visit Windows

The following visit windows will be used in the summarization or analysis of data. If the subject's last non-missing data point falls within the window, even if additional data points fall within the window, then that last data point will be used. Else, if more than 1 data point falls within a window then the data point closest to the target day will be used. If there are 2 data points equidistant to the target day, one high and one low, then the high data point will be used. Visit windowing will not be applicable to follow-up visits. If a subject terminates the study early, all assessments collected at the Early Termination visit will be assigned to the next scheduled visit (per Schedule of Assessments for the parameter) where the assessment would have been collected.

If Baseline is Day 1, then:

Day 15 (target day = 15) 2 - 21 and no randomization

Week 4 (target day = 29) 22 - 42 and no randomization

Week 8 (target day = 57) 43 - 70 and no randomization

Week 12 (target day = 85) 71 and above with no randomization

Week 13 (target day = 92) 78 - 95 and randomized

Week 14 (target day = 99) 96 - 102 and randomized

Week 15 (target day = 106) 103 - 109 and randomized

Week 16 (target day = 113) 110 - 119 and randomized

Week 18 (target day = 127) 120 - 133 and randomized

Week 20 (target day = 141) 134 - 147 and randomized

Week 22 (target day = 155) 148 - 161 and randomized

Week 24 (target day = 169) 162 and above (randomized and not a follow-up visit)

8.5. Pooling of Centers

Analyses will not include study site as a factor in the model. Region (North America and Europe) will be included, so sites will not be pooled based on the number of subjects, but by region.

8.6. Subgroups

Subgroup analyses will be conducted on all efficacy endpoints, demographics, disposition and exposure for the following populations:

- Children (≥ 6 and < 12 years of age), Adolescents (≥ 12 and < 18 years of age), including Children and Adolescents combined (≥ 6 and < 18 years of age), and Adults (≥ 18 years of age)
- Region (North America and Europe)
- Males and Females
- Ethnicity

Additionally, Time from Randomization to a loss of ≥ 50% improvement on the YGTSS-TTS will also be analyzed using the following subgroups:

- Early Responders (at Week 4) and Later Responders (at Week 8)

9. Demographic, Other Baseline Characteristics and Medication

9.1. Subject Disposition and Withdrawals

Subject disposition will be presented for all subjects, which include the following:

- Number of subjects enrolled
- Number of screened and reason for screen failure
- Number (%) of subjects in the Safety Set
- Number (%) of subjects who discontinued study prematurely and their reason during open label
- Number (%) of subjects in the Pharmacokinetic Set
- Number (%) of subjects randomized (Intent-to-Treat Set)

Among the randomized subjects, the following will be summarized:

- Number (%) of subjects in the Modified Intent-to-Treat Set
- Number (%) of subjects in the Per-Protocol Set
- Number (%) of subjects who completed the study
- Number (%) of subjects who discontinued study prematurely and their reason during R/WD

A separate by-subject listing of subject disposition and withdrawal will also be provided. Subjects who screen failed will be listed along with the date and reason for the screen failure.

Randomized subjects not included in an analysis set and their reason for exclusion will be summarized and listed.

9.2. Demographic and Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the Safety, Modified Intent-to-Treat, and Intent-to-Treat Sets by randomized treatment and overall. Summary statistics and by-subject listings will be provided.

Demographics and baseline characteristics will include age, sex, ethnicity, weight, height, body mass index (BMI), weight z-score, height z-score, BMI z-score for children/adolescents and for adults. Medical History and Concomitant Diseases

9.3. Medical History and Concomitant Diseases

Medical history will be summarized by system organ class (SOC) and preferred term using the number and percentage of subjects with each term and will be produced from the Safety Set. Medical history will be sorted alphabetically by SOC and in descending order of number of subjects per preferred term within each SOC.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or higher.

A separate by-subject listing of medical history will also be provided.

9.4. Medication

Prior and concomitant medications will be summarized based on classification using the Anatomical Therapeutic Chemical (ATC) classification and preferred drug name from the World Health Organization Drug Dictionary, version Mar 2019, or later.

9.4.1. Prior Medication

Prior medications are defined as medications entered in the eCRF that either start, or end before the first dose of study medication. Prior medications will be summarized using the number and percentage of subjects by ATC (4th level, or most specific level available if 4th level is unavailable) and preferred drug name for the Safety Set.

Prior medications which continue after first dose of study medication will also be classified as a concomitant medication.

9.4.2. Concomitant Medication

Concomitant medications are defined as medication on the eCRF that are taken on or after or are ongoing at the start date of dosing. Concomitant medications will be summarized using the number and percentage of subjects by ATC (4th level, or most specific level available if 4th level is unavailable) and preferred drug name for the Safety Set.

9.5. Extent of Exposure

Duration of exposure in days will be summarized using descriptive statistics by open-label stabilization and double-blind randomized withdrawal period (by treatment group and overall) and overall. The duration of exposure in days will also be categorized (<7, ≥7, ≥14, ≥28, ≥56, ≥84, ≥91, ≥98, ≥105, ≥112, ≥126, ≥140, ≥154, ≥168), and tabulated.

A listing including study drug administration information from the eCRF will be presented.

9.6. Treatment Compliance

Subjects are expected to take study medication as per dosing regimen specified in section 4.5.

Subjects will be considered compliant overall for study medication if the compliance is ≥80%. Descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) for number of actual tablets taken and number of expected tablets taken will be summarized by treatment group. Treatment compliance will be summarized descriptively as a continuous variable as well as a categorical variable (<80%, 80%-120%, >120%) by treatment group.

10. Efficacy

10.1. Primary Efficacy Endpoint and Analysis

The YGTSS is a clinician-rated, multi-dimensional instrument for assessing tic symptoms in children and adults with TD. It includes a semi-structured interview with either caregivers (for subjects <18 years of age) or adult subjects (≥ 18 years of age) and clinical observations that assess tic and tic-related impairment severity over the previous week. Every attempt should be made, per subject, to complete interview by the same caregiver or subject and same rater for all visits.

Both motor and vocal tics are assessed for symptom number, frequency, intensity, complexity, and interference on a 0–5 Likert scale. Scores from each dimension are totaled to reflect the severity of motor tics (range 0–25), vocal tics (range 0–25) and combined tics, or Total Tic Score (-TSS) (range 0–50). A separate tic-related impairment scale, scored from 0 to 50, is also included and calculated for the Global Severity score (-GS).

YGTSS will be assessed at Screening, Baseline and at Weeks 4, 8, 12, 13, 14, 15, 16, 18, 20, 22, 24 and 7 day follow up visit.

The primary efficacy endpoint is time from Randomization to Relapse defined as a loss of ≥ 50% of the improvement experienced on the YGTSS-TTS from Baseline to the last visit in the open-label Stabilization period (Week 12), or initiation of additional medications to treat symptoms of TD, or requirement of hospitalization for worsening symptoms of TD in subjects ≥ 6 and < 18 years during the double-blind R/WD period for ecopipam compared to placebo. Data from subjects who complete or discontinue from the double-blind R/WD period without Relapse will be considered as censored observations. The log rank test will be the primary test of statistical significance. Kaplan-Meier curves will be used to compare the times to relapse between the treatment groups. The hazard ratio and its 95% confidence interval (CI) will be estimated from the Cox proportional hazard model with treatment as a factor. The proportional hazards assumption will be evaluated graphically and analytically, for example by assessing martingale and Schoenfeld residuals and by modeling time-dependent covariates.

The analysis of the primary efficacy endpoint will be performed in the mITT (primary), ITT, and PP populations according to the randomized treatment.

10.1.1. Sensitivity Analysis

To assess the robustness of the primary efficacy analysis, the following sensitivity analysis will be performed for the mITT and the ITT set:

Assume subjects who are lost to follow up or who discontinue the study for reasons other than Relapse or lack of efficacy meet the Relapse criteria. Their last non-missing date on study will be used as the date of Relapse. Relapse rate will be estimated using Kaplan-Meier methods and the difference between treatment arms will be tested using the log rank test. Cox proportional hazard model will be run with treatment as factor.

10.2. Secondary and Exploratory Efficacy Endpoints and Analyses

All secondary and exploratory efficacy endpoints will be analyzed in the mITT population and ITT population according to randomized treatment. A hierarchical (fixed-sequence) testing approach will be

used for the analysis of the selected efficacy endpoints to maintain the experiment-wise type I error rate of 5%. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be carried out on the remaining hypotheses, and remaining hypotheses testing will be considered exploratory rather than confirmatory.

The order of testing following the primary efficacy endpoint is outlined below:

Secondary Efficacy Endpoint

- Time from Randomization (Week 12) to Relapse in all subjects irrespective of age for ecopipam compared to those receiving placebo during the double-blind, R/WD period.

Exploratory Efficacy Endpoints which may be considered Secondary Efficacy Endpoints if there is a 100% Correlation with the Primary Efficacy Endpoint

- Time from Randomization (Week 12) to a worsening by at least one category of the Global Impression Tourette's Syndrome of Severity (CGI-TS-S) in subjects ≥ 6 and < 18 years for ecopipam compared to those receiving placebo during the double-blind, R/WD period.
- Time from Randomization (Week 12) to a worsening by at least one category of the CGI-TS-S in all subjects for ecopipam compared to those receiving placebo irrespective of age.

10.2.1. Time from Randomization (Week 12) to Relapse in all subjects irrespective of age for ecopipam compared to placebo during the double-blind R/WD period (Secondary Efficacy Endpoint)

Statistical analysis:

A secondary analysis will be performed irrespective of age. The analysis method will be the same as the primary efficacy analysis as described in Section 10.1.

10.2.2. Time from Randomization (Week 12) to a worsening by at least one category of the CGI-TS-S in subjects ≥ 6 and < 18 years for ecopipam compared to placebo during the double-blind, R/WD period

The Clinical Global Impression of Tourette Syndrome (CGI-TS) consists of two reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms. The severity scale (CGI-TS-S) ranges from 1 (Normal, not ill) to 7 (extremely ill). The improvement scale (CGI-TS-I) ranges from 1 (very much improved) to 7 (very much worse) with a score of 1 or 2 defining positive response.

The severity rating is based upon observed and reported symptoms, behavior, and function in the past seven days with the score reflecting the average severity level across the seven days. The efforts of peers, teachers and parents to assist, accommodate, or support the subject should be considered in overall severity.

Severity will be assessed at Screening, Baseline and at Weeks 4, 8, 12, 13, 14, 15, 16, 18, 20, 22 and 24. Improvement will be assessed at Baseline and at Weeks 4, 12, 13, 14, 15, 16, 18, 20, 22 and 24.

The Severity scale ranges from : 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients where the improvement scale ranges from : 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6= much worse; 7=very much worse."

Statistical analysis:

This is a time-to-event endpoint not related to Relapse which will rely on a treatment policy strategy. A cumulative incidence approach will be used to account for the competing risk of study discontinuation due to Relapse. Gray's test will be used to test for a statistically significant treatment difference (Gray 1988). Cause-specific Cox proportional hazards regression model will be used to obtain the hazard ratio and its 95% CI for time to worsening (Cox 1972). In this model, subjects who complete or discontinue from the double-blind randomized withdrawal period before meeting endpoint criteria (worsening by at least one category of the CGI-TS-S) and for reasons not related to Relapse (such as Adverse Event, Pregnancy etc. as captured in eCRF) will be censored at the time of discontinuation.

The correlation in subjects ≥ 6 and < 18 years, between meeting relapse criteria based on YGTSS-TTS and having at least a 1-point reduction on CGI-TS-S will be assessed at the visit where relapse occurs. If there is a 100% correlation of this endpoint i.e. 100% of subjects who would have met Relapse criteria based on the YGTSS and at least 90% completed CGI-TS-S for subjects with completed YGTSS-TTS, also had at least a 1-point decrease on the CGI-TS-S (i.e. these two types of events occur simultaneously) then it may be considered as a secondary endpoint with agreement from Health Authorities. The strong correlation would suggest Relapse is not a competing risk.

10.2.3. Time from Randomization (Week 12) to a worsening by at least one category of the CGI-TS-S in all subjects for ecopipam compared to placebo irrespective of age.

Statistical analysis:

This analysis will be performed irrespective of age. The analysis method will be the same as the secondary efficacy analysis as described in Section 10.2.2.

The correlation in subjects, irrespective of age, between meeting relapse criteria based on YGTSS-TTS and those who had at least a 1-point reduction on CGI-TS-S will be assessed at the visit where relapse occurs. If there is a strong correlation of this endpoint i.e. 100% of subjects who would have met Relapse criteria based on the YGTSS and at least 90% completed CGI-TS-S for subjects with completed YGTSS-TTS, also had at least a 1-point decrease on the CGI-TS-S (i.e. these two types of events occur simultaneously) then it may be considered as a secondary endpoint with agreement from Health Authorities. The strong correlation would suggest Relapse is not a competing risk.

10.2.4. Mean change from Randomization (Week 12) to Week 24 in the YGTSS-TTS for ecopipam compared to placebo.

An exploratory analysis will be performed on the change in YGTSS-TTS from randomization to Week 24.

Statistical analysis:

The mean change from Randomization (Week 12) to Week 24 (Weeks 13,14,15,16,18,20, 22 and 24) in YGTSS-TTS will be summarized. This endpoint will be analyzed with a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17, 2=adults >=18) and covariate for week 12 YGTSS-TTS. Visit will include weeks 13,14,15,16,18, 20, 22 and 24. By visit comparisons will be provided. In the event the model does not converge using the standard unstructured covariance matrix, the Fisher scoring algorithm to obtain initial values of covariance parameters will be tried. If this method fails to converge, the FA0(T) structure will be tried. Following failure of this method, the successive univariate method proposed by Lu and Mehrotra (2010) will be tried. In the event all the previous methods fail to converge, the autoregressive and Toeplitz structures will be tried, and a sandwich estimator for the treatment effect estimate will be implemented. The final covariance structure will be documented in the table. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.5. Mean change from Randomization (Week 12) to Week 24 in the CGI-TS-S for ecopipam compared to placebo.

An exploratory analysis will be performed on the change in CGI-TS-S from randomization to Week 24.

Statistical analysis:

The mean change from Randomization (Week 12) to Week 24 (Weeks 13,14,15,16,18,20, 22 and 24) in CGI-TS-S will be summarized. This endpoint will be analyzed with a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17, 2=adults >=18) and covariate for week 12 CGI-TS-S. Visit will include weeks 13,14,15,16,18,20, 22 and 24. By visit comparisons will be provided. In the event the model does not converge using the unstructured covariance matrix, the methods described in Section 10.2.4 will be tried. The final covariance structure will be documented in the table. All observed endpoint data will be used in this analysis, without imputation. Summary statistics will be presented along with a full data listing by treatment group.

10.2.6. Mean change from Randomization (Week 12) to Week 24 in the YGTSS-Global Severity (GS) Score for ecopipam compared to placebo.

An exploratory analysis will be performed on the change in YGTSS-Global score (GS) from randomization to Week 24.

Statistical analysis:

The mean change from Randomization (Week 12) to Week 24 (Weeks 13,14,15,16,18,20, 22 and 24) in YGTSS-GS will be summarized. This endpoint will be analyzed with a Mixed Model for Repeated

Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17, 2=adults >=18) and covariate for week 12 YGTSS-GS. Visit will include weeks 13,14,15,16,18,20, 22 and 24. By visit comparisons will be provided. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.7. Mean change from Randomization (Week 12) to Week 24 in the Caregiver Global Impression of Change (CaGI-C) for ecopipam compared to placebo.

The CaGI-C scale is an 8-point Likert scale for subjects < 18 years old that asks the caregiver the following question: overall, how have the patient's symptoms changed (if at all) since the beginning of the study (before starting treatment)? The CaGI-C is rated as follows: 0 (Not rated), 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse, 6 (much worse), and 7 (very much worse).

CaGI-C will be assessed at Weeks 4, 12, 18 and 24.

Derived Variables and Statistical analysis:

The mean change from Randomization (Week 12) to Week 24 (Weeks 18 and 24) in CaGI-C will be summarized. This endpoint will be analyzed with a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17) and covariate for week 12 CaGI-C. Visit will include weeks 18 and 24. By visit comparisons will be provided. In the event the model does not converge using the unstructured covariance matrix, the methods described in Section 10.2.4 will be tried. The final covariance structure will be documented in the table. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.8. Time from Randomization (Week 12) to loss of ≥ 50% of the improvement from Baseline (Day 1) experienced on the YGTSS-TTS at the last visit (Week 12) in the open-label Stabilization period

Statistical analysis:

An exploratory analysis will be performed on subjects with YGTSS-TTS. The analysis method will be similar to the primary efficacy analysis as described in Section 10.1. Data from subjects who complete or discontinue from the double-blind R/WD period without loss of ≥ 50% of the improvement will be considered as censored observations. The log rank test will be the primary test of statistical significance. Kaplan-Meier curves will be used to compare the times to loss of ≥ 50% of the improvement between the treatment groups. The hazard ratio and its 95% confidence interval (CI) will be estimated from the Cox proportional hazard model with treatment as a factor.

10.2.9. Mean change from Randomization (Week 12) to Week 24 in the Clinical Global Impression of Tourette Syndrome Improvement (CGI-TS-I) for ecopipam compared to placebo.

An exploratory analysis will be performed on the change in CGI-TS-I from randomization to Week 24.

Statistical analysis:

The mean change from Randomization (Week 12) to Week 24 (Weeks 13,14,15,16,18,20, 22 and 24) in CGI-TS-I will be summarized. This endpoint will be analyzed with a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17, 2=adults >=18) and covariate for week 12 CGI-TS-I. Visit will include weeks 13,14,15,16,18,20, 22 and 24. By visit comparisons will be provided. In the event the model does not converge using the unstructured covariance matrix, the methods described in Section 10.2.4 will be tried. The final covariance structure will be documented in the table. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.10. Mean change from Randomization (Week 12) to Week 24 in the Premonitory Urge for Tics Scale (PUTS).

The PUTS is a 9-item self-report questionnaire measuring premonitory sensations in individuals with tics. In this study, the rater will read the questions to 6-17- year-old subjects and record their responses. Each item is scored from 1 (not at all true) to 4 (very much true). Thus, total scores range from 9 to 36, and higher scores represent greater premonitory urges, indicative of worst severity. An exploratory analysis will be performed on the change in PUTS score from randomization to Week 24.

Derived Variables and Statistical analysis:

The total score is computed by summing the 9 items without imputing missing values. The score will be calculated only if all the questions are answered. Thus, total scores range from 9 to 36, and higher scores represent greater premonitory urges, indicative of worst severity. The mean change from Randomization (Week 12) to Week 24 (Weeks 18 and 24) in PUTS will be summarized. This endpoint will be analyzed with a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17) and covariate for week 12 PUTS. Visit will include weeks 18 and 24. By visit comparisons will be provided. In the event the model does not converge using the unstructured covariance matrix, the methods described in Section 10.2.4 will be tried. The final covariance structure will be documented in the table. All observed endpoint data will be used in this analysis, without imputation. Summary statistics will be presented along with a full data listing by treatment group.

10.2.11. Mean change from Baseline (Day 1) to Week 24 in Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) score for ecopipam compared to placebo.

Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) is a patient-reported health related quality of life measure developed for children and adolescents. The C&A-GTS-QOL is a 27-item questionnaire specific to TS patients that asks the patient to assess the extent to which their quality of life is impacted by their symptoms. The C&A-GTS-QOL contains 4 subscales (psychological, physical/activities of daily living (ADL), obsessive-compulsive, and cognitive) and uses a 5 point Likert scale ranging from no problem to extreme problem. Higher scores indicate worse symptom severity. The instrument includes a visual analogue scale used to express the extent of self-satisfaction about life. Higher scores indicate greater satisfaction. Patients will also be asked how satisfied they feel overall with their life at that moment by using a Visual Analogue Scale (VAS) scale between 0 and 100.

Derived Variables and Statistical Analysis:

Following are the questions assessed in each C&A GTS QOL subscale:

- Psychological (questions 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27)
- Physical/ADL (questions 1, 2, 3, 4, 5, 6, 26)
- Obsessive-compulsive (questions 7, 8, 9, 10,15)
- Cognitive (questions 11, 12, 13, 14)

Scores for the four subscales are generated by summing items and, for ease of interpretation, transformation to a range of 0 to 100 (100x [(observed score - min possible score)/ (max possible score - min possible score)]). The total score, resulting from the sum of the subscale scores, is also normalized to a 0–100 range. If a response to at least 1 question within subscale is missing, then the missing responses will not be replaced, and the subscale score will be set to missing; if at least 1 subscale is missing then the total score will be set to missing. For all analysis and summary, transformed scores will be used.

An exploratory analysis will be performed on the change in C&A-GTS-QOL total score and VAS from Baseline to Week 24.

The mean change from Baseline (Day 1) to Week 24 in C&A-GTS-QOL will be summarized. The VAS, subscales and total score will be analyzed with a fixed effects model using the SAS MIXED procedure. The model will include fixed effects for treatment, region, age group (0 = children 6-11, 1 = adolescents 12-17) and covariate for baseline C&A-GTS-QOL. All observed endpoint data will be used in this analysis.

Summary statistics for the VAS, subscales, and total score will be presented along with a full data listing by treatment group.

10.2.12. Mean change from Baseline (Day 1) to Week 24 in Gilles de la Tourette Syndrome–Quality of Life Scale (GTS-QOL) score in adults for ecopipam compared to placebo.

See section 10.2.11 for a description of the Gilles de la Tourette Syndrome–Quality of Life Scale (GTS-QOL). An exploratory analysis will be performed on the change in GTS-QOL VAS and total score from Baseline to Week 24.

Statistical analysis:

The VAS, subscales and total score will be analyzed with a fixed effects model using the SAS MIXED procedure. The model will include fixed effects for treatment, region, and covariate for baseline C&A-GTS-QOL. All observed endpoint data will be used in this analysis.

Summary statistics for the VAS, subscales, and total score will be presented along with a full data listing by treatment group.

10.2.13. Mean change from Baseline (Day 1) to Week 12 in the YGTSS-TTS.

See section 10.1 for a description of the YGTSS-TTS. An exploratory analysis will be performed on the change in YGTSS-TTS from Baseline to Week 12.

Statistical analysis:

The mean change from Baseline (Day 1) to Week 12 (Week 4, 8 and 12 open-label) in YGTSS-TTS will be calculated. The paired t-test will be used for analyzing the change from baseline. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics will be presented along with a full data listing.

10.2.14. Percentage of subjects with a decrease in their YGTSS-TTS by 25% or greater at any time point from Baseline (Day 1) to Week 12.

Statistical analysis:

The percent of subjects with a 25% or greater improvement on the YGTSS-TTS score at any time between the Baseline visit to the Week 12 visit (Week 4, 8 and 12) will be considered as a Response. Any subject who has at least 1 Response (>=25% improvement) will be considered as a Responder; otherwise, the subject will be considered a Non-Responder.

Summary statistics for visit week 4, week 8, week 12 and overall will be presented along with a full data listing.

In addition, the percent of subjects who have maintained Responder status from the previous visit (i.e., responder at Week 4 and still a responder at Week 8) will be presented.

Similar analyses will be performed for 50%, 75%, and 100% improvement.

10.2.15. Mean change from Baseline (Day 1) to Week 24 in the YGTSS-TTS for ecopipam compared to placebo.

See section 10.1 for a description of the YGTSS-TTS. An exploratory analysis will be performed on the change in YGTSS-TTS from Baseline to Week 24 (Weeks 4, 8, 12, 13, 14, 15, 16, 18, 20, 22 and 24).

Statistical analysis:

The analysis method for the YGTSS-TTS will be analyzed with a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17, 2=adults >=18) and covariate for baseline YGTSS-TTS. Visit will include weeks 4, 8, 12, 13,14,15,16,18,20, 22 and 24. By visit comparisons will be provided. In the event the model does not converge using the unstructured covariance matrix, the methods described in Section 10.2.4 will be tried. The final covariance structure will be documented in the table. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.16. Mean change from Baseline (Day 1) to Week 24 in the YGTSS-GS for ecopipam compared to placebo.

See section 10.1 for a description of the YGTSS-GS. An exploratory analysis will be performed on the change in YGTSS-TTS from Baseline to Week 24 (Weeks 4, 8, 12, 13, 14, 15, 16, 18, 20, 22 and 24) .

Statistical analysis:

The analysis method for the YGTSS-GS score will be analyzed with a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17, 2=adults >=18) and covariate for baseline YGTSS-GS. Visit will include weeks 4, 8, 12, 13,14,15,16,18,20, 22 and 24. By visit comparisons will be provided. In the event the model does not converge using the unstructured covariance matrix, the methods described in Section 10.2.4 will be tried. The final covariance structure will be documented in the table. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.17. Mean change from Baseline (Day 1) to Week 24 in the Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) for ecopipam compared to placebo.

See section 10.2.2 for a description of the CGI-TS-S. An exploratory analysis will be performed on the change in CGI-TS-S score from Baseline to Week 24 (Weeks 4, 8, 12, 13, 14, 15, 16, 18, 20, 22 and 24)

Statistical analysis:

The analysis method for the CGI-TS-S score will be analyzed with a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17, 2=adults >=18) and covariate for baseline CGI-TS-S. Visit will include weeks 4, 8, 12, 13,14,15,16,18,20, 22 and 24. By visit comparisons will be provided. In the event the model does not converge using the unstructured covariance matrix, the methods described in Section 10.2.4 will be tried. The final covariance structure will be documented in the table. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.18. Caregiver Global Impression of Change (CaGI-C) through Week 24 for ecopipam compared to placebo.

See section 10.2.7 for a description of the CaGI-C. An exploratory analysis will be performed on the CaGI-C through Week 24 (Weeks 4, 12, 18 and 24).

Derived Variables and Statistical analysis:

CaGI-C rating will be categorized as Improved (1 (very much improved), 2 (much improved), 3 (minimally improved), No change and Worsened (5 (minimally worse, 6 (much worse), and 7 (very much worse)). All observed endpoint data will be used in this analysis, without imputation. Chi-Square test will be used to compare between treatment group.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.19. Mean change from Randomization (Week 12) to Week 24 in the Change in Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) for ecopipam compared to placebo.

See section 10.2.11 for a description of the C&A-GTS-QOL. An exploratory analysis will be performed on the change in C&A-GTS-QOL score from Week 12 to Week 24.

Statistical analysis:

The analysis method for the C&A-GTS-QOL score will be analyzed with a fixed effects model using the SAS Mixed procedure. The model will include fixed effects for treatment, region, age group (0 = children 6-11, 1 = adolescents 12-17) and covariate for week 12 C&A-GTS-QOL. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics for the VAS, subscales, and total score will be presented along with a full data listing by treatment group.

10.2.20. Clinical Global Impression of Tourette Syndrome Improvement (CGI-TS-I) through Week 24 for ecopipam compared to placebo.

See section 10.2.2 for a description of the CGI-TS-I. An exploratory analysis will be performed on the change in CGI-TS-I score through Week 24 (Weeks 4,12,13, 14, 15, 16, 18, 20, 22 and 24).

Derived Variables and Statistical analysis:

CGI-TS-I rating will be categorized as Improved (1 (very much improved), 2 (much improved), 3 (minimally improved), No change and Worsened (5 (minimally worse, 6 (much worse), and 7 (very much worse)). All observed endpoint data will be used in this analysis, without imputation. Chi-Square test will be used to compare between treatment group.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.21. Time from Randomization (Week 12) to treatment discontinuation during the double-blind R/WD period for ecopipam compared to placebo.

Statistical analysis:

An exploratory analysis will be performed on all randomized subjects in R/WD period to find time from randomization to study or treatment discontinuation. The analysis method will be similar to the primary efficacy analysis as described in Section 10.1. Data from subjects who complete the study will be considered as censored observations. The log rank test will be the primary test of statistical significance. Kaplan-Meier curves will be used to compare the times to treatment discontinuation between the treatment groups. The hazard ratio and its 95% confidence interval (CI) will be estimated from the Cox proportional hazard model with treatment as a factor. All observed endpoint data will be used in this analysis, without imputation.

10.2.22. Time from Randomization (Week 12) to loss of ≥ 100% of the improvement experienced on the YGTSS-TTS from Baseline (Day 1) to the last visit (Week 12) in the open-label Stabilization period for ecopipam compared to placebo.

Statistical analysis:

An exploratory analysis will be performed on all randomized subjects in R/WD period. The analysis method will be similar to the primary efficacy analysis as described in Section 10.1. Data from subjects who complete or discontinue from the double-blind R/WD period without loss of ≥ 100% of the improvement will be considered as censored observations. The log rank test will be the primary test of statistical significance. Kaplan-Meier curves will be used to compare the times to loss of ≥ 100% of the improvement between the treatment groups. The hazard ratio and its 95% confidence interval (CI) will be estimated from the Cox proportional hazard model with treatment as a factor. All observed endpoint data will be used in this analysis, without imputation.

10.2.23. Mean change from Randomization (Week 12) to Week 24 in the YGTSS subscales (Motor, Vocal, and Impairment) for ecopipam compared to placebo.

An exploratory analysis will be performed on the change in each of the YGTSS subscales from randomization to Week 24.

Statistical analysis:

The mean change from Randomization (Week 12) to Week 24 (Weeks 13,14,15,16,18,20, 22 and 24) in each of the YGTSS subscales will be summarized. This endpoint will be analyzed with a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17, 2=adults >=18) and covariate for week 12 YGTSS subscale score. Visit will include weeks 13,14,15,16,18, 20, 22 and 24. By visit comparisons will be provided. In the event the model does not converge using the unstructured covariance matrix, the methods described in Section 10.2.4 will be tried. The final covariance structure will be documented in the table. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.24. Mean change from Baseline (Day 1) to Week 24 in the YGTSS subscales (Motor, Vocal, and Impairment) for ecopipam compared to placebo

An exploratory analysis will be performed on the change in each of the YGTSS subscales from Baseline to Week 24 (Weeks 4, 8, 12, 13, 14, 15, 16, 18, 20, 22 and 24).

Statistical analysis:

The analysis method for each of the YGTSS subscale scores will be a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure with REPEATED statement. The model with an unstructured covariance matrix will include fixed effects for treatment, visit, interaction between treatment and visit, region, age group (0 = children 6-11, 1 = adolescents 12-17, 2=adults >=18) and covariate for baseline YGTSS subscale score. Visit will include weeks 4, 8, 12, 13,14,15,16,18,20, 22 and 24. By visit comparisons will be provided. In the event the model does not converge using the unstructured covariance matrix, the methods described in Section 10.2.4 will be tried. The final covariance structure will be documented in the table. All observed endpoint data will be used in this analysis, without imputation.

Summary statistics will be presented along with a full data listing by treatment group.

10.2.25. Sensitivity Analysis

For exploratory endpoints of mean change, the difference in means between treatment arms in change from Randomization (Week 12) to Week 24 or from Baseline (Day 1) to Week 24, a sensitivity analysis may be performed. For the intercurrent events of study treatment discontinuation due to lack of efficacy, treatment related adverse events, death prior to Week 24 and Relapse for subjects with no assessment at

Week 24, the non-collected data of assessment at Week 24 will be multiply imputed using similar subjects (relevant demographic/baseline characteristics) from the placebo arm.

For example, the exploratory efficacy analysis on change in the YGTSS-TTS from Randomization (Week 12) to week 24 (Weeks 13, 14, 15, 16, 18, 20, 22 and 24) is to use MMRM model using all observed data. This model is appropriate when data are missing at random (MAR). To assess the robustness of the primary efficacy analysis, the following additional sensitivity analyses for missing data will be included for the mITT set:

1. Missing at Random (MAR) predictive mean matching multiple imputation method
2. Missing Not at Random (MNAR) jump to reference multiple imputation method
3. Tipping point under MNAR assumption

Details of sensitivity analysis for missing data and the statistical model are explained below.

10.2.25.1. Sensitivity analyses for missing data

Details of sensitivity analyses for missing data includes MAR predictive mean matching multiple imputation method, MNAR jump to reference multiple imputation method, and MNAR tipping point analysis are as follows:

1) MAR predictive mean matching multiple imputation method

All missing data will be imputed for patients missing data at week 24 using the predictive mean matching multiple imputation method (Heitjan and Little 1991, Schenker and Taylor 1996) for a MAR data assumption using fully conditional specification (FCS) method. The imputation model will include age group at baseline, region, treatment arm, week 12 YGTSS-TTS, and YGTSS-TTS at all visits up to week 24 (Weeks 13, 14, 15, 16, 18, 20, 22 and 24) where the YGTSS is scheduled to be collected. This imputation will be performed using the SAS MI procedure with fcs specification. The resulting complete, imputed datasets will each be analyzed using the same model as the exploratory analysis of mean change model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002). The SAS code for the multiple imputation methodology is detailed in the Appendix (Section 16.2).

2) MNAR jump to reference multiple imputation method

Data will be imputed for patients missing data at week 24 using similar predictive mean matching multiple imputation method. Under a MNAR data assumption, patients will have their missing data at week 24 imputed as if they behaved like placebo treated patients after dropout. Only placebo patients with complete data will be included in the imputation model. The imputation models will include age group at baseline, region, week 12 YGTSS-TTS score, and YGTSS-TTS scores at all visits up to week 24 (Weeks 13, 14, 15, 16, 18, 20, 22 and 24) where the YGTSS is scheduled to be collected. After obtaining complete data sets, the complete data sets will be used in the analysis. The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002). The SAS code for the multiple imputation methodology is detailed in the Appendix (Section 16.3).

3) Tipping point analysis:

In the event that statistical significance in favor of ecopipam is determined from the primary analysis, subjects in the ecopipam group with a missing YGTSS-TTS score (change from randomization) will be assigned successively more extreme values, whilst subjects in the placebo group with a missing YGTSS-TSS score (change from randomization) will be assigned successively less extreme values, to find the point at which statistical significance is lost (i.e. the 2-sided P-value becomes greater than 0.05 or significance is in favor of placebo).

Details for tipping point analysis are described below:

a. For patients that completed the study, intermittent missing data are considered as MAR and will be imputed by predictive mean matching multiple imputation method (Heitjan and Little 1991, Schenker and Taylor 1996). The imputation model will include age group at baseline, region, treatment arm, week 12 TTS score, and TTS scores at all visits up to the imputed visit where the TTS is scheduled to be collected.

b. For patients who discontinued due to any reason, all missing data will be imputed using the same predictive mean matching multiple imputation method. The imputed values will be adjusted under MNAR assumption:

    - Patients randomized to ecopipam: the first missing value after patients dropout will be analyzed assuming the unobserved outcome is on average worsened by δ1 (where δ1 = 1 to 10 or estimated treatment effect (MAR model), whichever is higher, in step of 1) compared to the patients who have no missing value;

    - Patients treated by placebo: the first missing value after patients dropout will be analyzed assuming the unobserved outcome is on average better by δ2 (where δ2 = 1 to 10 or estimated treatment effect (MAR model), whichever is higher, in step of 1) compared to the patients who have no missing value;

    The penalty or reward will not be applied to the values from later time points as these values are penalized or rewarded through condition on previous time points. For each combination of (δ1, δ2), 100 imputed datasets will be obtained.

c. The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002).

The complete multiple imputation methodology, along with SAS code, is detailed in Appendix (Section 16.4).

11. Pharmacokinetics

Blood samples will be collected to measure concentrations of ecopipam and its major (active) metabolites at Weeks 4 and 8 or Week 12 if the 8 PK assessment is missed, during the open-label Stabilization period.

For the Week 4 visit, subjects and parents/caregivers (as applicable) will be instructed to skip the study medication on the evening prior to the Week 4 visit and to record the date and time that their last dose of study medication was taken. The study drug administration will occur on the day of the Week 4 visit at the site under the supervision of the study investigator. An intravenous catheter will be placed, and the subject will have samples collected at the following time windows: one sample at predose (34 to 44 hours since the last dose), one sample between 0.5 and 1.5 hours after administration of study medication, and one sample between 2 and 4 hours after study drug administration. Any samples should be collected at least 30 min apart.

For the Weeks 8 or 12 visit, subjects and parents/caregivers (as applicable) will be asked to record the date and time that their last dose of study drug administration was taken. A blood sample for PK will be collected. The time of sample collection will be recorded. Blood samples will be processed as outlined in the laboratory manual and analyzed for concentration of ecopipam and its major metabolite N -desmethylecopipam (EBS-101-40853).

To characterize the pharmacokinetics (PK) of ecopipam in all subjects: Plasma concentration-time data will be summarized in the Clinical Study Report (CSR). Population pharmacokinetic and pharmacodynamic analyses will be conducted and summarized separately, using data from this study along with data from other studies. The methodology for analyses will be reported in a separate analysis plan.

12. Safety

The population used for safety analyses will be the Safety Set (SS). Safety will be assessed by monitoring and recording all adverse events (AEs) and Serious Adverse Events (SAEs) (all Visits), regular monitoring of hematology, blood chemistry, and urine values (Screening, Baseline, Week 12, Week 18 and Week 24 Completion or Relapse/Early Termination, and 7- and 14-day Follow Up visits). HbA1c will be measured at Baseline, Week 12 and at Week 24 Completion or Early Termination visits. Regular measurement of vital signs and the performance of a physical examination will occur at every visit. An ECG will be performed at Screening, Baseline and Weeks 4, 12, 18, and 24 after supine BP is collected and at the 7-day and 14-day Follow Up visits. An additional assessment will include the Columbia-Suicide Severity Rating Scale (C-SSRS) (all Visits except 30 day Follow up visit). The Screening/Baseline version will be administered at Screening and the Since Last Visit version of the scale will be administered at all subsequent visits. Additional safety outcomes (Baseline and Weeks 4, 8, 12, 13, 14, 15, 16, 18, 20, 22 and 24) will include the Children's Depression Rating Scale-Revised (CDRS-R), the Pediatric Anxiety Rating Scale (PARS), the Extrapyramidal Symptom Rating Scale (ESRS), the Swanson, Nolan, and Pelham (SNAP-IV-26) questionnaire, the Children's Yale-Brown Obsessive Compulsive Scale-II (CY-BOCS-II), the Patient Health Questionnaire-9 (PHQ-9), the Hamilton Rating Scale for Anxiety (HAM-A), the Conners' Adult ADHD Rating Scale (CAARS) and the Yale-Brown Obsessive-Compulsive Scale-II (Y-BOCS-II) . The C-SSRS and ESRS will be administered to all age groups whereas PARS, SNAP-IV-26, CY-BOCS-II and CDRS-R will be applicable for only children and adolescent subjects. The Y-BOCS-II, PHQ-9, CAARS and HAM-A will be administered to only adult subjects (>=18 years of age).

All safety data will be summarized using the Safety Set according to the actual treatment.

Treatment-emergent adverse events (TEAEs) are defined as adverse events that are newly occurring or worsening after the first dose of study medication. The incidence of TEAEs will be summarized by treatment group, by severity and by relationship to study medication. Serious TEAEs and TEAEs leading to the study termination will be summarized by treatment group. Laboratory data, vital sign, physical examination, and ECG will be summarized by treatment and visit.

Timing-specific adverse events are defined as any adverse events that occur or increase in intensity during any specifically defined study milestones: Up-titration (Week 1-4), open-label maintenance (Weeks 5-12), double-blind R/WD (Weeks 13-16), double-blind R/WD (Weeks 17-24), Down-titration (Post Week 24 or early termination) The incidence of Up-titration and open-label maintenance phase AEs will be summarized for Ecopipam and double-blind R/WD and Down-titration AEs will be summarized by treatment group, by severity and by relationship to study medication and will be displayed such that comparisons can be made. The C-SSRS, CDRS-R, PARS, ESRS, SNAP-IV-26 questionnaire, CY-BOCS-II, PHQ-9, HAM-A, CAARS and Y-BOCS-II will also be summarized descriptively.

12.1. Adverse Events / Adverse Drug Reactions

An adverse event (AE) is any untoward medical condition that occurs in a patient while participating in this clinical study. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA 25.0 or later) terminology and the severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), v4.03, where applicable. An adverse drug reaction (ADR) means any AE caused by a drug or biologic.

A Clinical Adjudication Committee (CAC) will review selected treatment emergent neurological adverse events that are known to occur as the result of dopamine receptor antagonists (see Appendix 16.5). The details of the CAC procedures and adjudication process will be reported in a CAC charter.

Treatment-Emergent Adverse Events (TEAEs) are those adverse events/adverse drug reactions that are recorded during or following the initiation of study treatment administration, and do not necessarily have a causal relationship to the use of the study medication. Treatment-Emergent Adverse Events (simply referred to as adverse events in summary tables) will be summarized.

The following adverse event summary tables will be summarized by treatment group:

1) An overall summary with the number and percentage of patients reporting AEs, serious AEs (SAEs), maximum severity AEs, treatment-related AEs, treatment related SAEs, AEs leading to study treatment discontinuation and AEs with outcome of deaths.

2) AEs overall and by system organ class and preferred term.

   In this summary, a patient is counted once at the system organ class and once at each preferred term within the system organ class.

3) AEs overall and by system organ class, preferred term and initial daily dose level.

4) AEs overall and by system organ class, preferred term and region.

5) AEs overall and by system organ class, preferred term and weight band.

6) AEs overall and by system organ class, preferred term and time within the titration phase of open-label stabilization period. In all summaries by time the time windows are based on time since fist dose of ecopipam and will be as follows: 1-7, 8-14, 15-21, 22-28, 29-56, 57-84, 85-91, 92-98, 99-105, 106-112, 113-126, 127-140, 141-154, 155-168, 169-175, 176-184.

7) AEs overall and by system organ class, preferred term and time within open-label stabilization period.

8) AEs overall and by system organ class, preferred term and time within the double-blind randomized withdrawal period.

9) AEs overall and by system organ class, preferred term and time within the safety follow up.

10) AEs overall and by system organ class, preferred term and maximum severity.

    In this summary, a patient is counted once at the highest severity for which the event occurred in the system organ class and the highest severity for each unique preferred term within that system organ class. Therefore, patients may only contribute once to each preferred term and once to each system organ class.

11) Study-treatment-related AEs overall and by system organ class and preferred term.

All those AEs with relationship to treatment marked as “Possibly Related” or “Probably Related” or missing will be reported in the table.

12) Study-treatment related AEs by system organ class, preferred term and maximum severity

13) AEs leading to study treatment termination by system organ class and preferred term.

14) AEs leading to study treatment termination by system organ class, preferred term and maximum severity.

15) AEs by maximum severity, maximum relatedness and milestones (Up-titration, Open-label maintenance, double-blind R/WD (Weeks 13-16), double-blind R/WD (Weeks 17-24) and Down-titration).

A Serious Adverse Event (SAE) is an AE which falls into one or more of the following categories:

- Results in death.
- It is immediately life-threatening.
- It requires in-subject hospitalization or prolongation of existing hospitalization.
- It results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Serious adverse events will be summarized by treatment group and combined over both treatment groups. A summary by age group (Children (≥ 6 and < 12 years of age), Adolescents (≥ 12 and < 18 years of age), and Adults (≥ 18 years of age)) will also be provided.

16) SAEs overall and by system organ class and preferred term.

In this summary, a patient is counted once at the system organ class and once at each preferred term within the system organ class.

17) Treatment related SAEs overall and by system organ class and preferred term.
18) Adverse events of special interest (AESI) summary tables will include weight gain, extra-pyramidal reactions (AESIs associated with Dopamine blockade/dopamine antagonists) and suicidal ideations and behavior. More details are in section 16.5. These summaries will include severity, relatedness, and timing with respect to first dose of ecopipam.

19) Most common AEs (>= 5%) experienced during treatment period will be summarized by preferred term.

12.2. Laboratory Evaluations

Blood samples for hematology, chemistry, prolactin and urine samples for urinalysis are to be collected at screening, Baseline, Weeks 12 and 18, Completion [Week 24] or Relapse/Early Termination and 7 day and 14 day Follow Up visits. All results will be provided using International System of Units (SI). HbA1c will be measured at the baseline, week 12 and week 24 completion or early termination visits.

Descriptive statistics for hematology, chemistry, prolactin and HbA1c will be provided for each test parameter and for change from baseline treatment by visit and for each treatment group. Shift tables (i.e., low-normal-high at Baseline versus low-normal-high at each post-baseline visit in a 3-by-3 contingency table) will be provided for hematology, chemistry, prolactin, HbA1c and urine to assess changes from Baseline in laboratory values by visit for each treatment group. Shift (0.5% change) from baseline will be summarized for HbA1c by visit for each treatment group.

Separate listings will be provided for all laboratory evaluations (hematology, chemistry, prolactin, HbA1c and urinalysis.

12.3. Vital Signs

Vital sign measurements including blood pressure (after being supine for 5 minutes), pulse, height (children and adolescents only) and weight at each scheduled visit (Screening, Baseline, Weeks 4, 8, 12, 13, 14, 15, 16, 18, 20, 22 and 24 and the 7- and 14-day Follow Up visits) will be summarized with descriptive statistics at each scheduled time point by treatment group.

Changes from baseline for blood pressure and weight will be summarized with descriptive statistics at each scheduled time point by treatment group. Weight will be displayed in kilograms; height will be displayed in centimeters. Shift (0.5 change ranging from <-3 to >3) from baseline will be summarized for weight z-score, height z-score and bmi-z score by visit for each treatment group. Shift (increase or decrease at least 7% change) from baseline will be summarized for weight by visit for each treatment group.

All vital signs data will be presented in a listing.

12.4. ECG

The following ECG data will be collected at the Screening, Baseline, Weeks 4, 12, 18, and 24 and at the 7-and 14-day Follow Up visits:

- PR interval (msec)
- QRS interval (msec)
- QT interval
- QTc interval (msec)
- Overall ECG result (Normal; Abnormal)

An ECG is optional at unscheduled visits, per the investigator's discretion. All ECGs are monitored, interpreted, reported, and analyzed by a core central facility.
All findings will be presented in the ECG listings.

ECG analysis will consist of:

- Change from baseline for HR, PR, QRS, and QTcF for each treatment group. (QT and QTcB data will be in listings)
- Shift from baseline in overall ECG result.
- Treatment-emergent morphology findings will be listed.
- Categorical outlier analysis for HR, PR, QRS and QTcF by treatment group. The following categorical outliers will be summarized:

Adults:

ECG interval	Categorical outlier criteria
QTcF	Treatment-emergent value of > 450 and ≤ 480 ms when not present at baseline (new onset)
	Treatment-emergent value of > 480 and ≤ 500 ms when not present at baseline (new onset)
	Treatment-emergent value of > 500 ms when not present at baseline (new onset)
	Increase of QTcF from baseline of > 30 and ≤ 60 ms
	Increase of QTcF from baseline > 60 ms
PR	Increase of PR from baseline > 25% resulting in PR > 200 ms
QRS	Increase of QRS from baseline > 25% resulting in QRS > 120 ms
HR	Decrease of HR from baseline > 25% resulting in HR < 50 bpm
	Increase of HR from baseline > 25% resulting in HR > 100 bpm

Children and Adolescents:

ECG interval	Categorical outlier criteria
QTcF	Treatment-emergent value of > 450 and ≤ 480 ms when not present at baseline (new onset)
	Treatment-emergent value of > 480 and ≤ 500 ms when not present at baseline (new onset)
	Treatment-emergent value of > 500 ms when not present at baseline (new onset)
	Increase of QTcF from baseline of > 30 and ≤ 60 ms
	Increase of QTcF from baseline > 60 ms
PR	Increase of PR from baseline > 25% resulting in PR > 200 ms :- Adolescents (≥ 12 and < 18 years of age) PR > 180 ms :- Children (≥ 6 and < 12years of age)
QRS	Increase of QRS from baseline > 25% resulting in QRS > 110 ms :- Adolescents (≥ 12 and < 18 years of age) QRS > 100 ms :- Children (≥ 6 and < 12years of age)
HR	Decrease of HR from baseline > 25% resulting in HR < 50 bpm or HR > 100 bpm :- Adolescents (≥ 12 and < 18 years of age)

ECG interval	Categorical outlier criteria
	HR < 60 bpm or HR > 120 bpm :- Children (≥ 6 and < 12years of age)
	Increase of HR from baseline > 25% resulting in HR < 50 bpm or HR > 100 bpm :- Adolescents (≥ 12 and < 18 years of age) HR < 60 bpm or HR > 120 bpm :- Children (≥ 6 and < 12years of age)

12.5. Physical Examination

A Physical examination will be performed at every visit. This will include physical examination of the following body areas and systems: Head, Eyes, Ears, Nose, Mouth, Throat, Neck (including Thyroid); Thorax; Abdomen; Urogenital; Extremities; Neurological; Skin and Mucosae; and Other.

A physical exam is optional at unscheduled visits, per the investigator's discretion.

The Physical examination results will be summarized at each visit by treatment group. All physical examination data will be presented in a listing.

12.6. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a low burden (approximately 5 minutes for completion) instrument to assess both suicidal behavior and ideation. The scale is appropriate for subjects from age 6 through to an elderly population.

The number and percentage of subjects with suicidal behavior and ideation will be summarized by treatment group at all Visits except the 30-day Follow-up visit and all questionnaire data will be displayed in a listing.

12.7. Other Safety

12.7.1. Children's Depression Rating Scale-Revised (CDRS-R)

The CDRS-R is a clinically validated rating scale designed to assess psychiatric signs and symptoms of depressions. Fourteen signs and symptoms are rated from 1 being least severe (no difficulties) to 7 most severe (severe clinical difficulties), and 3 signs and symptoms are rated from 1 being least severe (no difficulties) to 5 most severe (severe clinical difficulties). The domains include social withdrawal, sleep disturbance, excessive fatigue, suicide ideation etc., aligned with the DSM-IV criteria for childhood depression.

Derived Variables and Statistical Analysis:

The raw summary score is the sum of all 17 items, ranging from 17 to 113. The score will be calculated only if all the questions are answered.

The raw summary score will be summarized by treatment group at Baseline and Weeks 4, 8, 12, 13, 14, 15, 16, 20, and 24 visits and all questionnaire data will be displayed in a listing.

A shift table (<40, >=40 and overall) will be provided for CDRS-R raw summary score to assess clinically meaningful changes from Baseline by visit for each treatment group.

12.7.2. Pediatric Anxiety Rating Scale (PARS)

The PARS is a clinician-rated instrument for assessing the severity of anxiety symptoms associated with common anxiety disorders and generalized anxiety in children and adolescents. The PARS has two sections: the symptom checklist and the severity items. The symptom checklist is used to determine the child's repertoire of symptoms during the past week.

Derived Variables and Statistical Analysis:

The 7-severity item is used to determine severity of symptoms and the PARS total score. Each severity item is coded from zero (none) to 5 (most extreme). Not applicable is coded to 8 and does not know is coded to 9. The total score for the PARS is total of the 7 severity items without imputing missing values. The total score ranges from 0 to 35. Codes "8" and "9" are not included in the summation.

The total score will be summarized by treatment group at the Baseline and Weeks 4, 8, 12, 13, 14, 15, 16, 20, and 24 visits and all questionnaire data will be displayed in a listing.

12.7.3. Extrapyramidal Symptom Rating Scale (ESRS)

The ESRS is a clinician-reported instrument developed to assess four types of drug-induced movement disorders: Parkinsonism, akathisia, dystonia, and tardive dyskinesia. For the subjective examination (subscale I of ESRS) scoring is on a four-point scale (0 = absent; 1=mild; 2=Moderate; 3 = severe).

Derived Variables and Statistical Analysis:

The subtotal ESRS I (sum of all 7-items without imputing missing values) will be summarized by treatment group at the Baseline and Weeks 4, 8, 12, 13, 14, 15, 16, 18, 20, 22 and 24 visits and all questionnaire data will be displayed in a listing.

All ESRS scores >= 1 will be adjudicated by the CAC and for any ESRS score >=1, the CAC will assign relatedness to the study drug.

12.7.4. Swanson, Nolan and Pelham (SNAP-IV) questionnaire

The SNAP-IV-26 questionnaire is designed to assess ADHD core symptoms of inattention (items 1-9), hyperactivity/impulsivity (items 10-18), and symptoms of oppositional defiant disorder (ODD) (items 19-26) in children and adolescents 6-18 years of age. In this study, 18-year-olds are defined as adults and will complete the CAARS-S:S adult scale. All 26 items are rated on 4-point scale and the total score ranges from 0-78, with higher scores indicating greater severity.

The SNAP-IV is based on a 0 to 3 rating scale: Not at All = 0, Just A Little = 1, Quite A Bit = 2, and Very Much = 3.

Derived Variables and Statistical Analysis:

Subscale scores on the SNAP-IV are calculated by summing the scores on the items in the subset and dividing by the number of items in the subset. The score for any subset is expressed as the Average Rating-Per-Item. Missing values will not be imputed.

The subscale scores will be summarized by treatment group at the Baseline and Weeks 4, 8, 12, 13, 14, 15, 16, 20, and 24 visits and all questionnaire data will be displayed in a listing.

12.7.5. Children's Yale-Brown Obsessive Compulsive Scale-II (CY-BOCS-II)

The CY-BOCS-II is a reliable and valid scale to both determine severity of OCD and to monitor improvement during treatment. The scale is a clinician-rated, 10-item scale (5 items regarding severity and 5 items regarding obsessions) that includes questions about the amount of time spent on obsessions/compulsions, level of impairment or distress, and how much resistance and control subjects have over these thoughts. The 10 items are assessed on a 6-point scale with an overall score.

Derived Variables and Statistical Analysis:

The total CY-BOCS-II score is computed as the sum of the consensus rating on items 1-10, range = 0 (no symptoms) to 50 (extreme symptoms), whereas the obsession and compulsion subtotals are the sums of items 1-5 and 6-10, respectively. Higher scores indicating more severe compulsions and obsessions. Missing values will not be imputed.

The total score will be summarized by treatment group at the Baseline and Weeks 4, 8, 12, 13, 14, 15, 16, 20, and 24 visits and all questionnaire data will be displayed in a listing.

12.7.6. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a validated, 9-question instrument to assess the degree of depression present in adults (18 years of age and older). The PHQ-9 incorporates DSM-4 depression diagnostic criteria with other leading major depressive symptoms into a brief, self-report questionnaire. The questionnaire rates the frequency of the symptoms which factors into the scoring severity index. Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation. The clinician will perform suicide risk assessment in subjects who respond positively to question 9. A follow-up, non-scored question screens and assigns weight to the degree to which depressive problems have affected the subject's level of function.

Derived Variables and Statistical Analysis:

As a severity measure, the PHQ-9 scores 9 items from 0 (not at all) to 3 (nearly every day) with total score range from 0 to 27.

The total score (sum of all items without imputing missing values) will be summarized by treatment group at the Baseline and Weeks 4, 8, 12, 13, 14, 15, 16, 18, 20, 22 and 24 visits and all questionnaire data will be displayed in a listing.

12.7.7. Hamilton Rating Scale for Anxiety (HAM-A)

The HAM-A is a clinician rated instrument for assessing the severity of anxiety symptoms in adults. The HAM-A consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe).

Derived Variables and Statistical Analysis:

Total scores range from 0 to 56 with higher scores indicating more severity.

The total score (sum of all items without imputing missing values) will be summarized by treatment group at the Baseline and Weeks 4, 8, 12, 13, 14, 15, 16, 20 and 24 visits and all questionnaire data will be displayed in a listing.

12.7.8. Conners' Adult ADHD Rating Scale- Self Report, Short Version (CAARS-S:S)

The CAARS is a 26-items self-report questionnaire assessing the severity of ADHD symptoms in adults. Subjects are asked to rate themselves on a range of symptoms anhd behaviors associated with ADHD in adults. Each item is scored on 4-point scale (0 = Not at all, never; 1 = Just a little, once in a while; 2 = Pretty much, often; and 3 = Very much, very frequently).

Derived Variables and Statistical Analysis:

Subscale raw scores are calculated by summing the scores on the items in the subset. The subscales (Inattention/Memory Problems, Hyperactivity/Restlessness, Impulsivity/Emotional Lability, Problems with Self-Concept, ADHD Index) will be summarized by treatment group at the Baseline and Weeks 4, 8, 12, 13, 14, 15, 16, 20, and 24 visits and all questionnaire data will be displayed in a listing.

12.7.9. Yale-Brown Obsessive Compulsive Scale-II (Y-BOCS-II)

The Y-BOCS-II is a 10-item clinician-rated measure of OCD symptom severity. Raters assess obsessions and compulsions separately in five domains: time spent, interference, distress, resistance, and control. Each domain is rated on a scale from 0 to 4. Total scores range from 0 to 40, with higher scores indicating greater symptom severity.

Derived Variables and Statistical Analysis:

The total score (sum of all items without imputing missing values) will be summarized by treatment group at the Baseline and Weeks 4, 8, 12, 13, 14, 15, 16, 20 and 24 visits and all questionnaire data will be displayed in a listing.

13. Interim Analysis

An interim analysis (IA) will be conducted after approximately 70% of Relapse events have accrued (34 Relapse events). The interim analysis will be performed by an independent statistician and governed by an independent Data Safety Monitoring Board (DSMB). The DSMB will consist of a physician experienced in the conduct of clinical studies (Chairman with TD experience), one clinician and one statistician experienced in TD will review the data at the interim analysis. The data will be cleaned by the data management group, and the analysis and reporting of the interim data to the DSMB will be the responsibility of an independent statistical group (which will not be directly involved in the conduct of the study). The DSMB will meet after the data presentation and issue recommendations. Minutes of the DSMB will be submitted to the sponsor after the study has been unblinded and will be appended to the final study report.

The 2-sided alpha level for the IA is 0.005. For the final analysis the 2-sided alpha level after IA spend will be 0.0492. If the statistical significance is reached at the IA, the DSMB can recommend stopping the study for overwhelming efficacy. However, the interim decisions for stopping for futility or potential sample size adjustments are based on the conditional power described below.

The primary efficacy endpoint is time from Randomization to Relapse defined as a loss of ≥ 50% of the improvement experienced on the YGTSS-TTS at the last visit in the open-label Stabilization period (Week 12), or initiation of additional medications to treat symptoms of TD, or requirement of hospitalization for worsening symptoms of TD in subjects ≥ 6 and < 18 years during the double-blind R/WD period for ecopipam compared to placebo. The analysis will be performed on all randomized subjects in R/WD period. The analysis method will be the same as the primary efficacy analysis as described in Section 10.1.

Assume that r is the number of Relapse events at interim analysis (r=34 in the planned interim analysis), R is the planned number of Relapse events (R=49) in this study, then the conditional power (CP) can be expressed as

$$CP=1-\Phi\left(Z_{int}\sqrt{\frac{r}{R-r}}+Z_{\alpha/2}\sqrt{\frac{R}{R-r}}+Z_{int}\sqrt{\frac{R-r}{r}}\right)$$

where $\Phi(.)$ denotes the cumulative distribution function of the standard normal distribution, and $z_{\alpha/2}$ denotes the $1-\alpha/2$ quantile of the standard normal distribution, and Z_{int} is z-value at interim analysis, which can be obtained from the output of PROC LIFETEST in SAS. The Z_{int} can be derived from the reported Logrank statistics and the corresponding covariance matrix

Derivation:

$$Z_{int}=\frac{O-E}{\sqrt{V}}=\frac{\sum_j(O_j-E_j)}{\sqrt{\sum_j V_j}}$$

where,

$O_j=d_{1j}$, Number of subjects in Ecopipam who developed Relapse, at distinct time j

$E_j = \left(\frac{Y_{1j}}{Y_j}\right) * d_j, \qquad d_j = d_{0j} + d_{1j}$, total number of Relapses at time j, Y_{1j} = Number of subjects in Ecopipam at time j,

Y_j = Number of subjects at risk at time j.

$V_j = \frac{Y_{0j}Y_{1j}d_j(Y_j - d_j)}{Y_j^2(Y_j - 1)}$, Y_{0j} = number of subjects at risk at time j at control arm,

$d_j = d_{0j} + d_{1j}$ total number of Relapses at both control arm and Ecopipam at time j.

Based on the results of the above conditional power and the promising zone approach [8], the DSMB may make the following interim decisions:

1) If p-value based on Logrank test at interim analysis is less than 0.005 and other measures (e.g., hazard ratio) imply a benefit of ecopipam over placebo, it is recommended to stop the study for overwhelming efficacy.
2) If 50%<CP<85%, then increase the number of required events such that CP based on the adjusted events ≥85% or reach the maximum number of Relapse events allowed, defined as two times the planned Relapse events (49 x 2 = 98).
3) If condition power (CP)<20%, it is recommended to stop the study for futility.
4) If all other cases, continue this study as planned.

No adjustment of the final alpha level will be required, other than the alpha spending of the IA, based on the CP approach.

Full details of the DSMB procedures including primary responsibilities of the DSMB, its relationship with other study components, its membership, and the purpose and timings of its meetings will be documented in a DSMB charter. These details will also include procedures to ensure confidentiality and proper communication, the guidelines to be implemented by the DSMB and an outline of the content of the closed reports (unblinded) and open reports (blinded) that will be provided to the DSMB.

14. Changes from Analysis Planned in Protocol

There are no changes from the analysis planned in protocol.

15. Reference List

1. Cox DR. Regression models and life tables. J Royal Stat Soc (series B). 1972;34:187-229.
2. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk, Annals of Statistics. 1988;16:1141-1154.
3. Heitjan, Daniel F., and Roderick J. A. Little. “Multiple Imputation for the Fatal Accident Reporting System.” Journal of the Royal Statistical Society. Series C (Applied Statistics), vol. 40, no. 1, 1991, pp. 13–29. JSTOR, www.jstor.org/stable/2347902.
4. Lu, K. and Mehrotra, D. Specification of covariance structure in longitudinal data analysis for randomized clinical trials, Stat Med. 2010; 29(4): 474-88.
5. Schenker, Nathaniel and Taylor, Jeremy M. G., (1996), Partially parametric techniques for multiple imputation, Computational Statistics & Data Analysis, 22, issue 4, p. 425-446.
6. Rubin, Donald B. (1987) Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons.
7. Little, R.J., & Rubin, D.B. (2002). Statistical Analysis with Missing Data, 2nd. ed. UNC 2011 SSIL Wiley
8. SAS Program (ages 0 to < 20 years) | Resources | Growth Chart Training | Nutrition | DNPAO | CDC
9. Mehta C, Pocock S. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 2011;30:3267–84.

16. Appendices

16.1. Schedule of Assessments

	Screening Period[a]	Open-Label Stabilization Period					Double-Blind Randomized Withdrawal Period Weeks 12 to 24 (Days 85 to 169)								Safety Follow-Up (Days 170-199)		
		Titration Phase		Maintenance Phase Weeks 4 to 12 (Day 29 up to 84)													
Visit/TC Study Day	**Screening VISIT 1 Day -28 to -1**	**Baseline VISIT 2 Day 1**	**W 2[f] Day 15 Telephone call only (±3d)**	**W4 / VISIT 3/ Day 29 (±3d)**	**W8 / VISIT 4 / Day 57 (±3d)**	**W 12 VISIT 5 Day 85 (±3d)**	**W13 / VISIT 6 / Day 92 (±3d)**	**W14 / VISIT 7 / Day 99 (±3d)**	**W15 / VISIT 8 / Day 106 (±3d)**	**W16 / VISIT 9 / Day 113 (±3d)**	**W18 / VISIT 10 / Day 127 (±3d)**	**W20 / VISIT 11 / Day 141 (±3d)**	**W22 / VISIT 12/ Day 155 (±3d)**	**W 24 VISIT 13 Day 169 or Relapse or ET (±3d)**	**7 Day F/U VISIT 14 (±3d)**	**14 Day F/U VISIT 15 (±3d)**	**30 Day F/U[f] Telephone call only (±3d)**
Informed Consent[a]	X																
DSM-5-TR Criteria for TD	X																
Inclusion/ Exclusion	X	X															
Medical/Psychiatric / Medication History	X	X															
Randomization						X											
Physical Exam/Vital Signs[b]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[b]	X	X		X		X					X			X	X	X	
Central Laboratory tests (Hematology, Chemistry, Urinalysis, HbA1c, Prolactin)[c]	X	X				X					X			X	X	X	

	Screening Period[a]	Open-Label Stabilization Period					Double-Blind Randomized Withdrawal Period Weeks 12 to 24 (Days 85 to 169)								Safety Follow-Up (Days 170-199)		
		Titration Phase		Maintenance Phase Weeks 4 to 12 (Day 29 up to 84)													
Visit/TC Study Day	**Screening VISIT 1 Day -28 to -1**	**Baseline VISIT 2 Day 1**	**W 2[f] Day 15 Telephone call only (±3d)**	**W4 / VISIT 3/ Day 29 (±3d)**	**W8 / VISIT 4 / Day 57 (±3d)**	**W 12 VISIT 5 Day 85 (±3d)**	**W13 / VISIT 6 / Day 92 (±3d)**	**W14 / VISIT 7 / Day 99 (±3d)**	**W15 / VISIT 8 / Day 106 (±3d)**	**W16 / VISIT 9 / Day 113 (±3d)**	**W18 / VISIT 10 / Day 127 (±3d)**	**W20 / VISIT 11 / Day 141 (±3d)**	**W22 / VISIT 12/ Day 155 (±3d)**	**W 24 VISIT 13 Day 169 or Relapse or ET (±3d)**	**7 Day F/U VISIT 14 (±3d)**	**14 Day F/U VISIT 15 (±3d)**	**30 Day F/U[f] Telephone call only (±3d)**
Central Urine Drug Screen	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Local Urine Pregnancy Test[i]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Yale Global Tic Severity Scale	X	X		X	X	X	X	X	X	X	X	X	X	X	X		
Clinical Global Impression – Tourette Syndrome Severity	X	X		X	X	X	X	X	X	X	X	X	X	X			
Clinical Global Impression – Tourette Syndrome Improvement				X		X	X	X	X	X	X	X	X	X			
Caregiver Global Impression of Change[h]				X		X					X			X			
Gilles de la Tourette Syndrome – Quality of Life Scale for Children and Adolescents[h]		X				X								X			
Gilles de la Tourette Syndrome – Quality of Life Scale[g]		X				X								X			

	Screening Period[a]	Open-Label Stabilization Period					Double-Blind Randomized Withdrawal Period Weeks 12 to 24 (Days 85 to 169)								Safety Follow-Up (Days 170-199)		
		Titration Phase		Maintenance Phase Weeks 4 to 12 (Day 29 up to 84)													
Visit/TC Study Day	**Screening VISIT 1 Day -28 to -1**	**Baseline VISIT 2 Day 1**	**W 2[f] Day 15 Telephone call only (±3d)**	**W4 / VISIT 3/ Day 29 (±3d)**	**W8 / VISIT 4 / Day 57 (±3d)**	**W 12 VISIT 5 Day 85 (±3d)**	**W13 / VISIT 6 / Day 92 (±3d)**	**W14 / VISIT 7 / Day 99 (±3d)**	**W15 / VISIT 8 / Day 106 (±3d)**	**W16 / VISIT 9 / Day 113 (±3d)**	**W18 / VISIT 10 / Day 127 (±3d)**	**W20 / VISIT 11 / Day 141 (±3d)**	**W22 / VISIT 12/ Day 155 (±3d)**	**W 24 VISIT 13 Day 169 or Relapse or ET (±3d)**	**7 Day F/U VISIT 14 (±3d)**	**14 Day F/U VISIT 15 (±3d)**	**30 Day F/U[f] Telephone call only (±3d)**
Premonitory Urge for Tics Scale		X		X		X					X			X			
Columbia Suicide Severity Rating Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Children's Depression Rating Scale – Revised[h]	X	X		X	X	X	X	X	X	X		X		X			
Pediatric Anxiety Rating Scale[h]		X		X	X	X	X	X	X	X		X		X			
Extrapyramidal Symptom Rating Scale		X		X	X	X	X	X	X	X	X	X	X	X			
Swanson, Nolan, and Pelham Questionnaire-IV-26[h]		X		X	X	X	X	X	X	X		X		X			
Children's Yale-Brown Obsessive Compulsive Scale-II[h]		X		X	X	X	X	X	X	X		X		X			
Patient Health Questionnaire-9[g]	X	X		X	X	X	X	X	X	X		X		X			

	Screening Period[a]	Open-Label Stabilization Period					Double-Blind Randomized Withdrawal Period Weeks 12 to 24 (Days 85 to 169)								Safety Follow-Up (Days 170-199)		
		Titration Phase		Maintenance Phase Weeks 4 to 12 (Day 29 up to 84)													
Visit/TC Study Day	**Screening VISIT 1 Day -28 to -1**	**Baseline VISIT 2 Day 1**	**W 2[f] Day 15 Telephone call only (±3d)**	**W4 / VISIT 3/ Day 29 (±3d)**	**W8 / VISIT 4 / Day 57 (±3d)**	**W 12 VISIT 5 Day 85 (±3d)**	**W13 / VISIT 6 / Day 92 (±3d)**	**W14 / VISIT 7 / Day 99 (±3d)**	**W15 / VISIT 8 / Day 106 (±3d)**	**W16 / VISIT 9 / Day 113 (±3d)**	**W18 / VISIT 10 / Day 127 (±3d)**	**W20 / VISIT 11 / Day 141 (±3d)**	**W22 / VISIT 12/ Day 155 (±3d)**	**W 24 VISIT 13 Day 169 or Relapse or ET (±3d)**	**7 Day F/U VISIT 14 (±3d)**	**14 Day F/U VISIT 15 (±3d)**	**30 Day F/U[f] Telephone call only (±3d)**
Hamilton Rating Scale for Anxiety[g]		X		X	X	X	X	X	X	X		X		X			
Conners' Adult ADHD Rating Scale[g]		X		X	X	X	X	X	X	X		X		X			
Yale-Brown Obsessive Compulsive Scale-II[g]		X		X	X	X	X	X	X	X		X		X			
PK Blood Draws[d,e]				X	X	X											
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Study Drug		X		X[d]	X	X				X		X		X			
Collect Unused Study Drug/Assess Drug Compliance				X	X	X	X	X	X	X	X	X	X	X	X		

Abbreviations: ADHD = attention-deficit hyperactivity disorder; AE = adverse event; BP = blood pressure; DSM-5-TR = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG = electrocardiogram; F/U = follow up; HR = heart rate; PK = pharmacokinetic(s); TD = Tourette's Disorder

[a] Informed consent must be obtained prior to any screening procedures. All screening procedures are to occur after confirmation of appropriate timeframe since discontinuation of applicable medications. Rescreening is allowed after approval by the Medical Advisor.

[b] Vital signs will include, pulse, BP (done 5 minutes after being supine and prior to the ECG), height and weight.

[c.] Subjects should be in a fasting state (8 hours) for laboratory tests. Fasting at the Screening visit is optional. HbA1c will be measured only at Baseline, Week 12, and Week 24 (completed subjects only).

[d.] At Week 4, ecopipam should be administered after the pre-dose blood draw. PK samples will be collected at 1) pre-dose; 2), post-dose between 0.5 and 1.5 hours; and 3) post-dose between 2 and 4 hours. Week 12 PK assessment only to be performed if Week 8 assessment is missed.

[e] If visits at Weeks 4, 8 and/or 12 are completed in locations other than study clinic due to restrictions because of the COVID-19 pandemic or other qualifying event, then collection of labs for PK assessments are optional.

[f] Week 2 and 30-Day FU visits will be a telephone call. If there are any abnormal findings, the subject will be brought to the site for full assessment. Subjects who complete the Baseline visit for the EBS-101-TD-391 open label extension study within 30 days of the Week 24 visit are not required to complete the 30-Day FU telephone call.

[g] Administration applicable to adult subjects only.

[h] Administration applicable to child and adolescent subjects only (6-17 years of age).

[I] For women of childbearing potential only. If positive, request a serum HCG on the Chemistry blood sample requisition form for confirmation of pregnancy.

16.2. MAR multiple imputation methodology

The FCS method will be used to impute missing values for TTS of the YGTSS change values and will use age group at baseline, region, treatment arm, week 12 YGTSS-TTS score and YGTSS-TTS scores at all visits up to week 24 to determine the scores (100 imputations will be created).

The SAS code for the imputation is as follows:

```
proc mi data=final out=mi1 seed=123 nimpute=100;
 class agegrp region arm ;
 var agegrp region arm wk12 _13 _14 _15 _16 _18 _20 _22 _24;
 fcs regpmm; run;
```

16.3. MNAR jump to reference multiple imputation methodology

The monotone method will be used to impute missing values for TTS of the YGTSS change values and will use age group at baseline, region, and week 12 TTS score to determine the scores (100 imputations will be created). Only placebo patients with complete data will be included in the imputation model.

The SAS code for the imputation is as follows:

```
proc mi data=final out=mi2 seed=123 nimpute=100;
class agegrp region arm;
  monotone reg;

  mnar model( _13 /modelobs=( arm='Placebo'));
  mnar model( _14 /modelobs=( arm='Placebo'));
  mnar model( _15 /modelobs=( arm='Placebo'));
  mnar model( _16 /modelobs=( arm='Placebo'));
  mnar model( _18 /modelobs=( arm='Placebo'));
  mnar model( _20 /modelobs=( arm='Placebo'));
  mnar model( _24 /modelobs=( arm='Placebo'));

  var agegrp region wk12 _13 _14 _15 _16 _18 _20 _22 _24;
run;
```

16.4. Tipping Point Analysis

Let delta1 and delta2 be the penalty to ecopipam group and reward for placebo group, respectively. Delta1 and delta2 = 1 to 10 (or estimated treatment effect from exploratory (mean change) analysis if it is larger than 10) in step of 1. General steps for this analysis includes:

Step 1:

For each combination of (delta1, delta2), 100 imputations will be created.

In order to induce monotonicity, an imputation model will first be used to impute missing values for TTS of the YGTSS week 13 change values and will use age group at baseline, treatment arm, and week 12 TTS score to determine the scores.

The SAS code for the imputation is as follows:

```
proc mi data=final out=mi seed=666 nimpute=100;
 class agegrp region1 arm;
 var agegrp region1 arm wk12 _13;
 monotone regpmm; run;

* Create delta1, delta2 in the dataset;

data mitv1;
 set mi;
 do i=1 to 10;
  do j=1 to 10;
     delta1=i; delta2=j; output;
  end;
 end;
run;

data mitv1;
 set mitv1;
 if firstdrp=13 and missdm in ("MNAR') and index(arm, 'ecopipam') then _&cv=_&cv+delta1;
else if firstdrp=13 and missdm in ("MNAR') and arm='Placebo' then _&cv=_&cv-delta2;
run;

* For each visit after week 13,
The macro % tippimp uses MNAR assumption where imputed values are adjusted:
Patients randomized to Ecopipam: the first missing value after patients dropout will be analyzed assuming the unobserved outcome is on average worsened by delta 1 compared to the patients who have no missing value; Patients randomized to Placebo: the first missing value after patients dropout will be analyzed assuming the unobserved outcome is better by delta 2 compared to the patients who have no missing value.;

%macro tippimp (cv, pv, pvs, seed);

proc mi data=mitv&pv out=mitv&currentv seed=&seed nimpute=1;
 class agegrp region1 arm;
 var agegrp region1 arm wk12 _&cv &pvs;
 monotone regpmm;
 by _Imputation_ &delta1 &delta2; run;
```

```
data mitv&cv;
if firstdrp=&cv and missdm in ("MNAR') and index(arm, 'ecopipam') then _&cv=_&cv+delta1;
else if firstdrp=&cv and missdm in ("MNAR') and arm='Placebo' then _&cv=_&cv-delta2;
run;
%mend;


% tippimp (14, 13, _13, 2626);
% tippimp (15, 14, 13%str(_13 _14), 2828);
% tippimp (16, 15, 14, 13%str(_13 _14 _15), 2929);
% tippimp (18, 16, 15, 14, 13%str(_13 _14 _15 _16), 3030);
% tippimp (20, 18, 16, 15, 14, 13%str(_13 _14 _15 _16 _18), 3131);
% tippimp (22, 20, 18, 16, 15, 14, 13%str(_13 _14 _15 _16 _18 _20), 3232);
% tippimp (24, 22, 20, 18, 16, 15, 14, 13 %str(_13 _14 _15 _16 _18 _20 _22), 3333);
```

Step 2

The resultant complete data sets will be analyzed using the same model as the exploratory (mean change) analysis. The SAS code is as follows:

```
proc sort data=mitv24; by delta1 delta2 _imputation_ descending arm avisitn; run;

proc mixed data=all order=data; by delta1 delta2 _imputation_;
  class usubjid arm avisitn agegrp region1;
  model chg=arm avisitn arm*avisitn agegrp region1 wk12 / ddfm=sat;
  repeated avisitn / type=un subject=usubjid;
  lsmeans arm*avisitn / diff cl;
  ods output diffs=diff(where=(avisitn=_avisitn) lsmeans=lsm; run;
```

Step 3

The results from the imputed data analysis will be combined using PROC MIANALYZE which will provide the LS mean and standard error of the LS mean for each treatment group at each visit as well as the LS mean difference, 95% CI and resultant p-value between the ecopipam and placebo groups at each visit. The SAS code is as follows:

```
proc sort data=diff; by delta1 delta2 avisitn arm; run;
proc sort data=lsm; by delta1 delta2 avisitn arm; run;

proc mianalyze data=diff;  by delta1 delta2 avisitn arm;
 modeleffects estimate;
 stderr stderr;
 ods output ParameterEstimates=estdiff; run;

proc mianalyze data=lsm; by delta1 delta2 avisitn arm;
 modeleffects estimate;
 stderr stderr;
 ods output ParameterEstimates=estlsm; run;
```

16.5. Adverse events of special interest (AESI)

Potential Adverse Events associated with dopamine antagonists

Symptomatic	**Psychiatric**	**Somatic**	**Neurologic**
1. Lethargy / Somnolence / Fatigue / Sedation 2. Dizziness / Lightheadedness / Vertigo 3. sleep disorder 4. Anxiety (Including major anxiety disorder) 5. Nausea / vomiting 6. Diarrhea 7. Sialorrhea 8. Constipation 9. Blurred vision	1. Suicidality 2. Depression (Major and Minor) 3. Psychosis 4. Obsessive / Compulsive behavior	1. Weight gain 2. Orthostatic hypotension 3. Temperature deregulation 4. Metabolic syndrome. 5. Elevated Glucose / HgA1c 6. Increased Total Cholesterol, increased LDL, decreased HDL, increased triglycerides 10. Leukopenia / neutropenia 11. QTc prolongation 12. Arrhythmias (supraventricular and ventricular) 13. Brady / Tachycardia 14. Elevated prolactin 15. Menstrual irregularities 16. Myocarditis / cardiomyopathy 17. Pancreatitis 18. Cholecystitis	1. Seizures 2. Syncope 3. Dystonia / dynamic dystonia 4. Akathisia 5 Rigidity 3. Bradykinesia 4. Tremor 5. Postural instability 6. Tardive dyskinesia 7. Tardive dyskinesia a/w withdrawal 8. Neuroleptic malignant syndrome 9. Oculogyric crisis

Neurological Adverse Events Triggering Adjudication

Neurologic Term	**Synonym 1**	**Synonym 2**	**Synonym 3**
Akathisia	Restlessness	Urge to move	
Ataxia	Incoordination	Clumsiness	
Bradykinesia	Slowness of movement		

Bruxism	Jaw Clenching		
Chorea	Involuntary movements	Muscle jerks	Extremity flinging
Dyskinesia	abnormal movements	dynamic dystonia	
Dysphagia	Swallowing difficulty		
Dysphonia	Vocal dysfunction	Abnormal posture	
Dystonia	Abnormal posture	Spasm	Contracture
Expressionless Facies	Decreased facial expression	Flat affect	
Gait disturbance	Unsteadiness	Falling, fear of	
Hyperkinesia	Agitation		
Oculogyric Crisis			
Postural Instability	Balance disorder		
Rigidity	Stiffness	Muscle tightness	Joint Tightness
Seizures	Loss of consciousness		
Syncope	Fainting		
Tremor	Resting tremor		