Statistical Analysis Plan for Interventional Studies

Sponsor Name: Emalex Biosciences, Inc.

Protocol Number: EBS-101-OL-001

Protocol Title:
A Multicenter, Open-Label, Extension Study Intended to Evaluate the Long-term Safety of Ecopipam Tablets in Children and Adolescent Subjects with Tourette's Syndrome

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

Approvals

Syneos Health Approval

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1. Glossary of Abbreviations

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIMS	Abnormal Involuntary Movement Scale
ATC	Anatomic Therapeutic Classification
BARS	Barnes Akathisia Rating Scale
BMI	Body Mass Index
C&A-GTS-QOL	Child and Adolescent Gilles De La Tourette Syndrome-Quality of Life Scale
CDRS-R	Children's Depression Rating Scale-Revised
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
CTCAE	Common Toxicity Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
HbA1c	Hemoglobin A1c
HCl	Hydrochloride
ITT	Intention-to-Treat set
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
PARS	Pediatric Anxiety Rating Scale
PO	Oral (per os)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
TS	Tourette's Syndrome

Abbreviation	Description
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 that 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 are responsible for the production and quality control of all tables, figures, and listings.

2.2. Timings of Analyses

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

3. Study Objectives

3.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of ecopipam tablets in pediatric subjects (aged ≥6 to ≤18 years at Baseline of the EBS-101-CL-001 study) with Tourette's Syndrome (TS) that were previously enrolled in the EBS-101-CL-001 study (Phase 2b) and completed the Phase 2b study.

3.2. Secondary Objective(s)

The secondary objective of this study is to evaluate the durability of effect of ecopipam in pediatric subjects (aged ≥6 to ≤18 years at Baseline of the EBS-101-CL-001 study) with TS.

3.3. Brief Description

This is an international, multicenter, open-label, long-term extension study evaluating the safety of ecopipam tablets for the treatment of children and adolescent subjects with TS. Subjects who completed the Phase 2b, randomized double-blind efficacy and safety study (EBS-101-CL-001) and who continue to meet the inclusion/ exclusion criteria for this study will be eligible to participate in this study. All subjects will be titrated to a target dose of 2 mg/kg/day as subjects participating from previous studies will be tapered down from study medication to maintain the blind. Subjects will complete study visits every month for 1 year. Follow Up visits will be conducted 7 and 14 days after the last dose of study medication and a Follow Up phone call will be conducted 30 days after the last dose of study medication. Study Visits may be completed in locations other than clinic and/or safety and efficacy assessments required at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event.

Safety will be monitored throughout the study at all visits by repeated monitoring of adverse events (AEs), vital signs, the Columbia-Suicide Severity Rating Scale (C-SSRS), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Pediatric Anxiety Rating Scale (PARS) and Children's Depression Rating Scale-Revised (CDRS-R). In addition to these assessments, at Baseline, Months 1, 3, 6, 9 and 12 safety will also be monitored by clinical and laboratory evaluations, and electrocardiogram (ECG) monitoring. In addition to the scales aforementioned, the Yale Global Tic Severity Scale (YGTSS), Clinician Global Impression of Tourette Syndrome of Severity (CGI-TS-S), the Clinician Global Impression Tourette Syndrome of Improvement (CGI-TS-I) and the Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) will also be assessed at Baseline, Months 1, 3, 6, 9 and 12. At the Follow Up visits, AE monitoring, the C-SSRS, clinical and laboratory evaluations and vital signs will be assessed. A Follow Up phone call will be conducted 30 days after the last dose of study medication to assess AEs. Subjects will be monitored for signs of abuse, and withdrawal or dependence.

3.4. Subject Selection

3.4.1. Inclusion Criteria

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

3.4.2. Exclusion Criteria

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

3.5. Determination of Sample Size

This is a one-year safety and tolerability study as a follow up to the double-blind study (EBS-101-CL-001) and number of subjects enrolled in this is dependent on the number of subjects completing that study.

3.6. Treatment Assignment

Since this is an open-label study, all subjects that have cleared the inclusion/exclusion criteria will be administered ecopipam HCl at a target dose of 2 mg/kg/day.

3.7. Administration of Study Medication

Ecopipam Hydrochloride (HCl) will be supplied as 12.5-, 37.5-, 50-, 75-, and 100-mg tablets. The target dose is 2 mg/kg via oral (per os) (PO) administration.

During the 4-week titration period, the following ecopipam HCl doses will be administered for each of the weight bands:

- Those who weigh ≥18-≤23 kg will titrate from 12.5 mg daily to 37.5 mg daily: 12.5 mg during Week 1, 25 mg (two 12.5-mg tablets) during Week 2, and 37.5 mg during Weeks 3 and 4.
- Those who weigh >23-≤34 kg will titrate from 12.5 mg daily to 50 mg daily: 12.5 mg during Week 1, 25 mg (two 12.5-mg tablets) during Week 2, 37.5 mg during Week 3, and 50 mg during Week 4.
- Those who weigh >34-≤44 kg will titrate from 12.5 mg daily to 75 mg daily: 12.5 mg during Week 1, 25 mg (two 12.5-mg tablets) during Week 2, 50 mg during Week 3, and 75 mg during Week 4.
- Those who weigh >44-≤68 kg will titrate from 25 mg daily to 100 mg daily: 25 mg (two 12.5-mg tablets) during Week 1, 50 mg during Week 2, 75 mg during Week 3, and 100 mg during Week 4.
- Those who weigh >68-≤83 kg will titrate from 25 mg daily to 150 mg daily: 25 mg (two 12.5-mg tablets) during Week 1, 50 mg during Week 2, 100 mg during Week 3, and 150 mg (two 75-mg tablets) during Week 4.
- Those who weigh >83 kg will titrate from 25 mg daily to 200 mg daily: 25 mg (two 12.5-mg tablets) during Week 1, 50 mg during Week 2, 100 mg during Week 3, and 200 mg (two 100-mg tablets) during Week 4.

During the treatment phase, the following ecopipam HCl doses will be administered for each of the weight bands:

- Those who weigh ≥18-≤23 kg will receive 37.5 mg daily.
- Those who weigh >23-≤34 kg will receive 50 mg daily.
- Those who weigh >34-≤44 kg will receive 75 mg daily.
- Those who weigh >44-≤68 kg will receive 100 mg daily.
- Those who weigh >68-≤83 kg will receive 150 mg daily.
- Those who weigh >83 kg will receive 200 mg daily.

All doses will be administered PO once daily in the evening.

At the end of the open-label treatment phase, subjects will titrate off therapy and receive ecopipam HCl doses that will be reduced by 25 mg/day until off of drug; signs of symptoms of withdrawal will be monitored.

Subjects with weight changes during the course of the study resulting in change in weight band may titrate to the dosing of the new weight band at the discretion of the Investigator and with the approval of the Medical Monitor. If approved, the dose of study medication should be increased according to the titration scheme noted for the new weight band.

3.8. Study Procedures and Flowchart

Subjects will complete study visits every month for 1 year. Follow Up visits will be conducted 7 and 14 days after the last dose of study medication and a Follow Up phone call will be conducted 30 days after the last dose of study medication.

See Appendix section 16.1 for the Schedule of Assessments.

4. Endpoints

4.1. Efficacy Endpoints

- Changes in the Yale Global Tic Severity Scale – Total Tic Score (YGTSS-TTS) from baseline to Months 1, 3, 6, 9, 12.
- Changes in the Yale Global Tic Severity Scale – Impairment (YGTSS-I) and Global (YGTSS-TTS + YGTSS-I = YGTSS-GS) from baseline to Months 1, 3, 6, 9, 12.
- Changes in Clinical Global Impression of Tourette Syndrome of Severity (CGI-TS-S) from Baseline to Months 1, 3, 6, 9, 12.
- Clinician Global Impression Tourette Syndrome of Improvement (CGI-TS-I) at Months 1, 3, 6, 9, 12.
- Changes in Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) from Baseline to Months 1, 3, 6, 9, 12.

4.2. Safety Endpoints

- Assessment of AEs or serious adverse event (SAEs) and their relationship to study drug (Unrelated, Possible Related, or Probably Related).
- Changes from baseline in clinical laboratory analysis (Hematology, Chemistry, Urinalysis and Hemoglobin A1c (HbA1c) assessments).
- Changes from baseline in vital signs.
- Changes from baseline in ECG.
- Changes from baseline in physical examination findings.

4.3. Other Safety Endpoints

- Changes from baseline in Columbia Suicide Severity Rating Scale (C-SSRS) results.
- Changes from baseline in Abnormal Involuntary Movement Scale (AIMS) results.
- Changes from baseline in Barnes Akathisia Rating Scale (BARS) results.
- Changes from baseline in Children's Depression Rating Scale-Revised (CDRS-R) results.
- Changes from baseline in Pediatric Anxiety Rating Scale (PARS) results.

5. Analysis Sets

5.1. Enrolled Set

The Enrolled Set will include all subjects who complete the Phase 2b, randomized double-blind efficacy and safety study (EBS-101-CL-001) and who continued to meet the inclusion and exclusion criteria and enrolled in this study. The Enrolled Set will be used for subject listings and summaries of subject disposition.

5.2. Safety Set

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

5.3. Modified Intent-to-Treat Set

The Modified Intention-to-Treat (mITT) set will consist of all subjects who receive at least one dose of study drug and have at least one post Baseline scoring of YGTSS. All efficacy analyses will be conducted using the mITT population.

5.4. Intention-to-Treat Set

The Intention-to-Treat (ITT) set will include all enrolled subjects. All efficacy analysis will also be conducted using the ITT population.

6. General Aspects for Statistical Analysis

6.1. General Methods

All analyses and outputs will be produced using SAS® version 9.4 or later. 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 frequency counts (n), and percentages.

All relevant subject data will be included in listings. All subjects entered 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.

6.2. Key Definitions

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

Duration of exposure is defined as (Date of Last Dose – Date of First Dose) +1. If 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 open-label treatment on Day 1.

Change from baseline will be calculated for the post-baseline assessment as post-baseline value – baseline value.

6.3. 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.

6.4. Visit Windows

The following visit windows will be used in the summarization or analysis of safety laboratory, vital signs, ECG, and physical exam data. If more than 1 data point falls within the 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 Baseline is Day 1, then:

Month 1 (target day = 29) 2 - 42

Month 2 (target day = 57) 43 - 70

Month 3 (target day = 85) 71 - 98

Month 4 (target day = 113) 99 - 126

Month 5 (target day = 141) 127 - 154

Month 6 (target day = 169) 155 - 182

Month 7 (target day = 197) 183 - 210

Month 8 (target day = 225) 211 - 238

Month 9 (target day = 253) 239 - 266

Month 10 (target day = 281) 267 - 294

Month 11 (target day = 309) 295 - 322

Month 12 (target day = 337) 323 and above (and not a follow-up visit)

For all efficacy and safety scales a modified last observation carried forward (LOCF) approach will be used to reassign Early Termination visits. Early Termination visits will be assigned to the next scheduled visit (per Schedule of Assessments for the parameter) after a subjects' latest scheduled visit before early termination.

6.5. 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.

6.6. Subgroups

Subgroups to be analyzed for select endpoints include age group (children 6-12 and adolescents 13-18) and region (North America and Europe).

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

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

- Number of subjects enrolled
- Number (%) of subjects in the Safety Set
- Number (%) of subjects in the Modified Intent-to-Treat Set
- Number (%) of subjects who completed the study
- Number (%) of subjects who discontinued study prematurely and their reason

A separate by-subject listing of subject disposition and withdrawal will also be provided.

7.2. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the Modified Intent-to-Treat and ITT Set. Summary statistics and by-subject listings will be provided.

Demographics and baseline characteristics will include age, sex, ethnicity, race, weight, height, body mass index (BMI).

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/m^2) = Weight(kg)/[Height$(m)^2$]

Demographics and baseline characteristics will also be summarized by treatment group (ecopipam, placebo and overall) from CL (EBS-101-CL-001) study.

7.3. Medical History

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

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher.

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

Medical History will also be summarized by treatment group (ecopipam, placebo and overall) from CL (EBS-101-CL-001) study.

7.4. **Medication**

All 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.

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

7.4.1. 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 by ATC level 2 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.

7.4.2. 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 by ATC level 2 and preferred drug name for the Safety Set.

8. Efficacy

The mITT as well as ITT set will be used for the analysis of the efficacy endpoints.

The YGTSS, CGI-TS-S, and C&A-GTS-QOL will be assessed at Baseline, Months 1, 3, 6, 9 and 12. The CGI-TS-I will be assessed at Months 1, 3, 6, 9 and 12.

8.1. Yale Global Tic Severity Scale (YGTSS)

The YGTSS is a clinician-completed rating scale used to quantify overall tic severity as well as specific subdomains of tic number, frequency, intensity, complexity and interference. Each of these subdomains is scored, on a 5-point scale, separately for motor and vocal tics and then summed across both motor and vocal tics to yield a total tic score (TTS) ranging from 0 to 50. The YGTSS also provides for an overall impairment rating (0 = ‘‘none’’ to 50 = ‘‘severe’’). Global YGTSS (YGTSS-GS) is the total of YGTSS-TTS and impairment score (YGTSS-I). Efficacy will be analyzed for the YGTSS-TTS, YGTSS-I and YGTSS-GS.

The observed YGTSS-TTS along with motor and phonic subdomains, YGTSS-I and YGTSS-GS values and their changes from baseline will be summarized by visit. The paired t-test will be used for analyzing the change from baseline within treatment.

The percent of subjects with a 25% or greater improvement on the YGTSS-TTS score at any time between the Baseline visit and post-baseline visit 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. Responder and Non-Responder will be summarized at each post-baseline visit and overall.

YGTSS-TTS will also be summarized by treatment group (ecopipam, placebo and overall) from CL (EBS-101-CL-001) study.

All YGTSS data will be presented in a listing.

8.2. Clinician Global Impression Tourette’s Syndrome of Improvement &Severity (CGI-TS-I &S)

The CGI consists of 2 reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms. The scale ranges from 1 = “very much improved” to 7 = very much worse” for the CGI-TS-I. The CGI severity scale (CGI-TS-S) will be used at each study site visit and ranges from 1 = “Normal, not ill at all” to 7 = “Extremely ill.”

The CGI-TS-S will be assessed at Baseline, Months 1, 3, 6, 9 and 12. The observed CGI-TS-S values and their changes from baseline will be summarized by visit. The paired t-test will be used for analyzing the change from baseline within treatment.

The CGI-TS-I will be assessed at Months 1, 3, 6, 9, and 12. The observed CGI-TS-I values will be summarized by visit.

All CGI-TS-I and CGI-TS-S data will be presented in a listing.

8.3. Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL)

C&A-GTS-QOL is a patient-reported health related quality of life measure developed for children and adolescents. Versions of the scale appropriate for subjects 6-12 years of age and 13-18 years of age will

be provided. Subjects who turn 13 during the course of the study should continue to be assessed using the version of the scale initially administered.

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 6 subscales (cognitive, coprophenomena, psychological, physical, obsessive-compulsive, and activities of daily living (ADL)) and uses a 5 point Likert scale ranging from no problem to extreme problem. Patients will also be asked how satisfied they feel overall with their life at that moment by using a Visual Analogue Scale (VAS) between 0 and 100 (Su et al 2017). Following are the questions assessed in each C&A GTS QOL subscale:

- Cognitive (questions 11, 12, 13, 14, 18, 20, 21, 23) (range: 0- 32)
- Psychological (questions 15, 16, 17, 19, 25, 27) (range: 0 – 24)
- Obsessive-compulsive (questions 7, 8, 9, 10) (range: 0 – 16)
- Physical (questions 1, 3, 4) (range: 0 – 12)
- Coprophenomena (questions 5, 6, 22) (range: 0 -12)
- ADL (questions 2, 24, 26) (range: 0-12)

Scores for the six 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. For C&A GTS-QOL, if a response to 1 question is missing within the subscale, the missing response will be replaced with the average of the remaining responses within the subscale; if responses to 2 or more questions within a subscale are missing, 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.

Summary statistics for the overall VAS score, QOL subscale scores for Cognitive, Psychological, Obsessive-compulsive, Physical, Coprophenomena, and ADL and QOL total score will be presented along with a full data listing by visit. The paired t-test will be used for analyzing the change from baseline within treatment. Mean C&A-GTS-QOL Change from Baseline Total Score and VAS Change from Baseline Score Over Time will be illustrated in a figure.

9. Safety

The population used for safety analyses will be the Safety Set (SS). Study Visits may be completed in locations other than clinic and/or safety and efficacy assessments required at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event. Safety will be monitored throughout the study at all visits by repeated monitoring of adverse events (AEs), vital signs, the Columbia-Suicide Severity Rating Scale (C-SSRS), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Pediatric Anxiety Rating Scale (PARS) and Children's Depression Rating Scale-Revised (CDRS-R). In addition to these assessments, at Baseline, Months 1, 3, 6, 9 and 12 safety will also be monitored by clinical and laboratory evaluations and electrocardiogram (ECG) monitoring. At the Follow Up visit, AE monitoring, the C-SSRS, clinical and laboratory evaluations and vital signs will be assessed. Laboratory evaluations will include hematology, chemistry, urine values and HbA1c. A Follow Up phone call will be conducted 30 days after the last dose of study medication to assess AEs. Subjects will be monitored for signs of abuse, and withdrawal or dependence. Additional assessments (all visits except the follow up visit) will include the AIMS, the BARS, the CDRS-R and the PARS. C-SSRS will also be assessed (all visits including the Follow Up visit).

All safety data will be summarized in Safety Set.

9.1. Extent of Exposure

Duration of exposure will be summarized using descriptive statistics. The duration of exposure will be categorized in months (<1, 1-<2, 2-<3, 3-<4, 4-<5, 5-<6, 6-<7 ,7-<8, 8-<9, 9-<10, 10-<11, 11-<12, ≥12 months) as well as in days (1-27, 28-55, 56-83, 84-111, 112-139, 140-167, 168-195, 196-223, 224-251, 252-279, 280-307, 308-335, ≥336). Duration of exposure (months) will be calculated as ((Date of Last Dose – Date of First Dose) +1)/30.25. If date of last dose is unknown, then the date of last clinical visit will be used.

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

9.2. Treatment Compliance

Subjects are expected to take study medication once per day.

Treatment compliance, as a percentage, will be calculated as compliance (%) = (Sum of Study drug taken= Yes) / (number of days in study) x 100. The number of actual doses taken will be recorded on the eCRF.

Subjects will be considered compliant overall for study medication if the compliance is ≥80%. Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) for number of actual tablets taken, number of expected tablets taken, and treatment compliance will be summarized.

9.3. Adverse Events (AEs)

An AE is any untoward medical condition that occurs in a subject while participating in this clinical study. The AEs will be coded to system organ class (SOC) and preferred term (PT) using the MedDRA dictionary, version 25.0. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 will be used to assess the severity of AEs.

All AEs that occur after the first study drug administration and up to 30 days after the subject's last study drug administration will be considered treatment-emergent adverse events (TEAEs).

Summaries will focus on the TEAEs (simply referred to as adverse events in summary tables). A subject with 2 or more TEAEs within the same level of summarization (i.e., SOC or PT) will be counted only once in that level using the most severe event or most related event.

Summaries presenting the frequency of AEs by SOC and PT will be sorted by descending frequency of SOC and then, within a SOC, by descending frequency of PT.

The following summary tables will be provided:

1) An overall summary with the number and percentage of patients reporting AEs, serious AEs, grade 3 or higher AEs, treatment-related AEs, AEs leading to study treatment discontinuation and AEs with outcome of deaths.

2) AEs and Treatment-Related Adverse Events (TRAEs) by maximum severity

3) AEs and Serious Adverse Events (SAEs) by maximum relatedness

4) AEs overall and by SOC and PT

5) AEs overall and by SOC, PT and highest CTCAE grade

6) TRAEs overall and by SOC and PT

7) TRAEs overall and by SOC, PT and highest CTCAE grade

8) AEs leading to study treatment termination overall and by SOC and PT

9) AEs leading to study treatment termination overall and by SOC and highest CTCAE grade

10) CTCAE Grade 3 or higher AEs, overall and by SOC and PT

11) SAEs overall and by SOC and PT

    A SAE is an AE which falls into one or more of the following categories:

    a. Results in death

    b. Is life-threatening

    c. Requires inpatient hospitalization or prolongation of existing hospitalization

    d. Results in persistent or significant disability or incapacity

    e. Is a congenital anomaly/birth defect

    f. Is any other important medical event

12) SAEs overall and by SOC and PT and by age group (children 6-12 and adolescents 13-18)

13) Adverse Event of Special Interests (AESIs) overall and by SOC and PT

Adverse Events of Special Interest (AESI) for ecopipam include Convulsions, Depression and Suicide/Self Injury, Drug Abuse, Dependence and Withdrawal, Dyslipedaemia, Hepatic Disorders, Hyperglycaemia/New Onset Diabetes Mellitus, NMS, and Psychosis and Psychotic Disorders.

AESI for Parkinsonism include Ataxia, Confusional state, Coordination abnormal, Somnolence, Disturbance in attention, Dyskinesia, Hyperkinesia, Gait disturbance, Memory impairment, Tremor, Vertigo, Agitation, Anxiety, Disturbance in attention, Dystonia, Bradykinesia, Musculoskeletal stiffness, Dysstasia, Gait disturbance, Posture abnormal, Balance disorder, Movement disorder, Movement disorder, Dyskinesia, Muscle rigidity, Coordination abnormal, Muscle contracture, Bradykinesia, Gait disturbance, Terminal insomnia, Nightmare, Poor quality sleep, Sleep disorder, Fatigue, Dizziness, Balance disorder, Restlessness, Amnesia, Confusional state, Dementia, Mental impairment, Speech disorder, Dysphonia, Vocal cord dysfunction, Parosmia, Anosmia, Urinary incontinence, Anxiety, Apathy, Joint stiffness, Reduced facial expression, Confusional state, Flat affect, Constipation, Depression, Dysphagia, Drooling, Fall, Fear of falling, Loss of visual contrast sensitivity, Muscle tightness, Dysgraphia, Dyskinesia, and Weight decreased.

AESI summary tables are listed below:

- AESI for ecopipam overall and by system organ class and preferred term
- AESI for Parkinsonism 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.

14) Most common AEs (>= 5%) first onset experienced during treatment period will be summarized by month and preferred term.

15) Most common AEs (>= 5%) new incidence or ongoing, experienced during treatment period will be summarized by month and preferred term.

9.4. Laboratory Evaluations

Blood samples for hematology and biochemistry are to be collected at Baseline, Months 1, 3, 6, 9 and 12 and One and Two Weeks Post Last Dose. Urine samples for urinalysis will be collected at Baseline, Months 1, 3, 6, 9 and 12. HbA1c will be measured at Months 1, 3, 6, 9 and 12. All results will be provided using International System of Units (SI).

Descriptive statistics for hematology, biochemistry, urinalysis and HbA1c will be provided for each test parameter and for change from baseline by visit. 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, biochemistry, urinalysis and HbA1c to assess changes from Baseline in laboratory values by visit. Shift (0.5% change ranging from <4.0% to >7.5%) from baseline will be summarized for HbA1c by visit. Also shift (<170, 170-199, >=200) from baseline for total cholesterol will be summarized by visit.

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

9.5. Vital Signs

Vital sign measurements including sitting systolic blood pressure, sitting diastolic blood pressure, sitting pulse rate, supine orthostatic systolic blood pressure, supine orthostatic diastolic blood pressure, supine pulse rate, standing orthostatic systolic blood pressure, standing orthostatic diastolic blood pressure, and standing pulse rate at each scheduled time and changes from baseline in vital sign measurements will be summarized with descriptive statistics at each scheduled time point.

Body height will be measured at Baseline and will be summarized. Weight will be measured at each schedule visit and, along with changes from baseline, will be summarized with descriptive statistics at each scheduled time point. Weight will be displayed in kilograms; height will be displayed in centimeters.

Body mass index (BMI) will be derived from the weight at each visit and from height (at screening), along with changes from baseline, will be summarized with descriptive statistics at each schedule timepoint.

BMI will be displayed in kilograms per meter squared.

The Centers for Disease Control and Prevention (CDC) growth charts will be used to calculate weight z-score, height z-score and BMI z-scores. 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. Mean BMI, height and weight z-scores over time will be illustrated in a figure.

Heart rate outliers such as >25% decrease change from baseline, <50, >25% decrease change from baseline and <50 as well as >25% increase change from baseline,>100, >25% increase change from baseline and >100 will be summarized by visit and overall.

All vital signs data will be presented in a listing.

9.6. ECG

The following ECG data will be collected at Baseline, Months 1, 3, 6, 9 and 12:

- PR interval (msec)
- QRS interval (msec)
- QT interval
- QTc interval (msec)
- Overall ECG result (Normal; Abnormal, Not Clinically Significant; Abnormal, Clinically Significant).

An ECG is optional at unscheduled visits, per the investigator's discretion.

The actual ECG results along with change from baseline will be summarized at each visit. Shift (<=450, >450 to <= 480, > 480 to <= 500, >500) from baseline in QTc interval will be summarized by visit. ECG outliers for QTc interval (change from baseline>30 to <=60, >60), PR interval (>25% increase change from baseline,>200, >25% increase change from baseline and PR>200) and QRS interval (>25% increase change from baseline,>200, >25% increase change from baseline and QRS>200) will be summarized by visit and overall. All ECG data will be presented in a listing.

9.7. Physical Examination

A Physical examination will be performed at Baseline, Month 1, 3, 6, 9 and 12 and One and Two Weeks Post Last Dose Follow Up visits. 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. All physical examination data will be presented in a listing.

9.8. **Other Safety**

9.8.1. 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 at all visits during the treatment, end of study/early termination and follow up visits.

All questionnaire data will be displayed in a listing.

9.8.2. Abnormal Involuntary Movement Scale (AIMS)

AIMS records the occurrences of tardive dyskinesia (TD) in subjects receiving neuroleptic medications. The test is used to detect TD and to follow the severity over time. It consists of rating the presence and severity of movement disorders involving the face, mouth, extremities, and trunk as well as three items of global judgment from a scale of 0 (none) to 4 (severe).

The AIMS total score will be calculated by summing the severity of the 10 items that are rated on a scale of 0 to 4. The total score will be summarized at Baseline, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12.

All questionnaire data will be displayed in a listing.

9.8.3. Barnes Akathisia Rating Scale (BARS)

BARS is used to assess the severity of drug-induced akathisia. Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness in the scale measure the level of subject's restlessness, ranging from zero (normal) to 3 (most severe) and are summed yielding a total score ranging from 0 to 9. The BARS also includes a global clinical assessment of akathisia, ranging from zero (absent) to 5 (severe).

The objective, subjective, total of objective and subjective scores and global scores will be summarized at Baseline and every month during treatment for one year. All questionnaire data will be displayed in a listing.

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

CDRS-R is a clinically validated rating scale designed to assess psychiatric signs and symptoms of depressions in children and adolescents. Fourteen signs and symptoms are rated from 1 (normal) to 7 (most severe), and 3 signs and symptoms are rated from 1 (normal) to 5 (most severe). The raw summary score is the sum of all 17 items, ranging from 17 to 113.

The raw summary score will be summarized at Baseline and every month during treatment for one year. All questionnaire data will be displayed in a listing.

9.8.5. Pediatric Anxiety Rating Scale (PARS)

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. PARS is a 7-item scale that 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. The total score ranges from 0 to 35. Codes "8" and "9" are not included in the summation.

The total score will be summarized at Baseline and every month during treatment for one year. All questionnaire data will be displayed in a listing.

9.9. **COVID-19 Analyses**

Due to COVID-19 pandemic, additional analyses will be conducted:

- Listings of COVID-19 related study disruptions by subject and by site, including descriptions of the disruption.
- Protocol deviations due to COVID-19 will be summarized by type in a table.

10. Changes from Analysis Planned in Protocol

As per protocol, the Modified Intention-to-Treat (mITT) set was defined as all subjects who receive at least one dose of study drug which is same as the safety population set. Hence the mITT set definition was updated as 'all subjects who receive at least one dose of study drug and have at least one post Baseline scoring of YGTSS'.

Following updates and additional analysis were included in the SAP after the data base lock.

- An additional analysis set, Intention-to-Treat (ITT) Set, was defined as all enrolled subjects. All efficacy analysis will also be conducted using the ITT population.
- Visit windowing will be used in the summarization or analysis of safety laboratory, vital signs, ECG, and physical exam data.
- For all efficacy and safety scales a modified last observation carried forward (LOCF) approach will be used to reassign Early Termination visits. Early Termination visits will be assigned to the next scheduled visit (per Schedule of Assessments for the parameter) after a subjects' latest scheduled visit before early termination.
- Demographics and baseline characteristics will also be summarized by treatment group (ecopipam, placebo, overall) from CL (EBS-101-CL-001) study in the mITT Set (Table 14.1.3.1a), and be also summarized for the ITT Set (Table 14.1.3.1b).
- Medical history will also be summarized by treatment group (ecopipam, placebo, overall) from CL (EBS-101-CL-001) study in the Safety Set (Table 14.1.3.2a).
- Extent of exposure summary by days will be provided as well (Table 14.1.5a).
- YGTSS-TTS will also be summarized by treatment group (ecopipam, placebo and overall) from CL (EBS-101-CL-001) study (Tables 14.2.1.1.1a).
- Efficacy summaries for the ITT Set will be generated (Tables 14.2.1.1.1b, 14.2.1.1.2b, 14.2.1.1.3b, 14.2.1.1.4b, 14.2.1.2b, 14.2.1.3b, and 14.2.1.4b).
- A summary of the percent of subjects with a 25% or greater improvement on the YGTSS-TTS in mITT set will be provided (Table 14.2.1.1.5).
- A summary of the most common (≥5%) AEs first onset by month will be provided in Table 14.3.1.9.1 and by month (new incidence or ongoing) in Table 14.3.1.9.2.
- Shifts from baseline summaries in BMI z-score, height z-score, and weight z-score will be generated and provided in Table 14.3.4.6a, Table 14.3.4.6b, and Table 14.3.4.6c, respectively. Mean BMI, height, and weight z-scores over time will be illustrated in Figure 14.3.4.6a, Figure 14.3.4.6b, and Figure 14.3.4.6c, respectively.
- A summary of shifts from baseline in 12-lead ECG QTc will be provided in Table 14.3.4.7a. A summary of outliers in 12-lead ECG will be provided in Table 14.3.4.7b.
- A summary of heart rate outliers will be provided in Table 14.3.4.7c.
- Shifts from baseline in HbA1c and total cholesterol will be provided in Table 14.3.4.8 and Table 14.3.4.9, respectively.

- Generation of listings for ITT Set: Listing 16.2.4.1b (demographics and baseline characteristics), Listing 16.2.6.1b (YGTSS), Listing 16.2.6.2b (CGI-TS), and Listing 16.2.6.3b (C&A-GTS-QOL).
- Generation of listings for Safety Set: Listing 16.2.9.1 (Height, Weight, and BMI z-scores).
- Generation of figures: mean changes from baseline for C&A-GTS-QOL total score (Figure 14.2.1.4.1a), mean changes from baseline for C&A-GTS-QOL VAS (Figure 14.2.1.4.1b), mean BMI, Height, Weight z-scores over time (Figures 14.3.4.6a, 14.3.4.6b and 14.3.4.6c).

11. Reference List

1. Su M, McFarlane F, Cavanna A, et al. The English Version of the Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL). J Child Neurol 2017;32(1):76-83.
2. SAS Program (ages 0 to < 20 years) | Resources | Growth Chart Training | Nutrition | DNPAO | CDC

12. Programming Considerations

12.1. General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format or portable document format pdf.
- Numbering of tables, figures, and listings (TFL) will follow ICH E3 guidance (or other logical order for studies performed according to GCP)

12.2. Table, Listing, and Figure Format

12.2.1. General

- All TFLs will be produced in landscape format, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

12.2.2. Headers

- All output should have the following header at the top left of each page:

  Emalex Biosciences, Inc
  Protocol EBS-101-OL-001

- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TFL is identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended. A decimal system (x.y and x.y.z) is used to identify TFLs with related contents. The title is centered. The analysis set is identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

12.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

12.2.5. Body of the Data Display

12.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Numbers containing fractional portions are decimal aligned.

12.2.5.2. *Table Conventions*

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
mild	3
moderate	8
severe	0

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean (SD)	XX.X (XX.XX)
Median	XX.X
Min, Max	XX, XX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999.
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.
- Unless otherwise specified, tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the overall group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subjects are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

12.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

12.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, and date the program was run (i.e., 'Program : myprogram.sas Table Generation: ddmmmyyyy).

13. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, and figures. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907)

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

14. Index of Tables

The following tables will be produced (table numbers and titles may be different in the final versions):

Header	Table Number	Name	Analysis Set
14.1		Demographic Data Summary Tables	
	14.1.1	Subject Disposition Summary	Enrolled Set
	14.1.2.1	Protocol Deviations Summary	Safety Set
	14.1.2.2	Protocol Deviations Due to COVID-19 Summary	Safety Set
	14.1.3.1	Demographics and Baseline Characteristics Summary	mITT Set
	14.1.3.1a	Demographics and Baseline Characteristics Summary by Treatment Group (CL)	mITT Set
	14.1.3.1b	Demographics and Baseline Characteristics Summary	ITT Set
	14.1.3.2	Medical History Summary	Safety Set
	14.1.3.2a	Medical History Summary by Treatment Group (CL)	Safety Set
	14.1.4.1	Prior Medications Summary	Safety Set
	14.1.4.2	Concomitant Medications Summary	Safety Set
	14.1.5	Extent of Exposure Summary	Safety Set
	14.1.5a	Extent of Exposure Summary	Safety Set
	14.1.6	Treatment Compliance Summary	Safety Set
14.2		Efficacy Data Summary Tables	
	14.2.1.1.1	YGTSS-TTS: Summary	mITT Set
	14.2.1.1.1a	YGTSS-TTS: Summary by Treatment Group (CL)	mITT Set
	14.2.1.1.1b	YGTSS-TTS: Summary	ITT Set
	14.2.1.1.2	YGTSS-TTS: Subscales Summary	mITT Set
	14.2.1.1.2b	YGTSS-TTS: Subscales Summary	ITT Set
	14.2.1.1.3	YGTSS-GS: Summary	mITT Set
	14.2.1.1.3b	YGTSS-GS: Summary	ITT Set
	14.2.1.1.4	YGTSS-Impairment: Summary	mITT Set
	14.2.1.1.4b	YGTSS-Impairment: Summary	ITT Set
	14.2.1.1.5	YGTSS-TTS: Subjects with a >= 25% Improvement	mITT Set
	14.2.1.2	CGI-TS-S: Summary	mITT Set
	14.2.1.2b	CGI-TS-S: Summary	ITT Set
	14.2.1.3	CGI-TS-I: Summary	mITT Set
	14.2.1.3b	CGI-TS-I: Summary	ITT Set
	14.2.1.4	C&A-GTS-QOL: Summary	mITT Set
	14.2.1.4b	C&A-GTS-QOL: Summary	ITT Set
14.3		Safety Data Summary Tables	
14.3.1		Adverse Events	
	14.3.1.1	Overall Summary of Adverse Events	Safety Set

Header	Table Number	Name	Analysis Set
	14.3.1.2.1	Summary of Adverse Events by Maximum Severity	Safety Set
	14.3.1.2.2	Summary of Adverse Events by Maximum Relatedness	Safety Set
	14.3.1.3.1	Summary of Adverse Events by System Organ Class and Preferred Term	Safety Set
	14.3.1.3.2	Summary of Adverse Events by System Organ Class, Preferred Term and Highest CTCAE Grade	Safety Set
	14.3.1.4.1	Summary of Treatment-Related Adverse Events by System Organ Class and Preferred Term	Safety Set
	14.3.1.4.2	Summary of Treatment-Related Adverse Events by System Organ Class, Preferred Term and Highest CTCAE Grade	Safety Set
	14.3.1.5.1	Summary of Adverse Events Leading to Treatment Termination by System Organ Class and Preferred Term	Safety Set
	14.3.1.5.2	Summary of Adverse Events Leading to Treatment Termination by System Organ Class, Preferred Term and Highest CTCAE Grade	Safety Set
	14.3.1.6	Summary of CTCAE Grade 3 or Higher Adverse Events by System Organ Class and Preferred Term	Safety Set
	14.3.1.7.1	Summary of Serious Adverse Events by System Organ Class and Preferred Term	Safety Set
	14.3.1.7.2	Summary of Serious Adverse Events by System Organ Class and Preferred Term by Age Group	Safety Set
	14.3.1.8.1	Summary of Adverse Events of Special Interest (AESI) for Parkinsonism by System Organ Class and Preferred Term	Safety Set
	14.3.1.8.2	Summary of Adverse Events of Special Interest (AESI) for Ecopipam by System Organ Class and Preferred Term	Safety Set
	14.3.1.9.1	Summary of Most common (>=5%) Adverse Event First Onset by Month	Safety Set
	14.3.1.9.2	Summary of Most common (>=5%) Adverse Events by Month (new incidence or ongoing)	Safety Set
14.3.4.1		Clinical Laboratory Data	

Header	Table Number	Name	Analysis Set
	14.3.4.1.1.1	Clinical Laboratory Results Summary: Hematology	Safety Set
	14.3.4.1.1.2	Shift from Baseline Summary: Hematology	Safety Set
	14.3.4.1.2.1	Clinical Laboratory Results Summary: Serum Chemistry	Safety Set
	14.3.4.1.2.2	Shift from Baseline Summary: Chemistry	Safety Set
	14.3.4.1.3.1	Clinical Laboratory Results Summary: Urinalysis	Safety Set
	14.3.4.1.3.2	Shift from Baseline Summary: Urinalysis	Safety Set
	14.3.4.1.4.1	Clinical Laboratory Results Summary: HbA1c	Safety Set
	14.3.4.1.4.2	Shift from Baseline Summary: HbA1c	Safety Set
14.3.4.2		Vital Signs	
	14.3.4.2.1	Vital Signs Summary	Safety Set
14.3.4.3		Electrocardiogram (ECG) Data	
	14.3.4.3.1	12-Lead Electrocardiogram Summary	Safety Set
	14.3.4.3.2	12-Lead Electrocardiogram Overall Interpretation Summary	Safety Set
14.3.4.4		Abnormal Physical Examination Results by Visit	
	14.3.4.4.1	Physical Examination Summary	Safety Set
14.3.4.5		Other Safety Data	
	14.3.4.5.1	Summary of Columbia Suicide Severity Rating Scale (C-SSRS)	Safety Set
	14.3.4.5.2	Summary of Abnormal Involuntary Movement Scale (AIMS) Total Score	Safety Set
	14.3.4.5.3	Summary of Barnes Akathisia Rating Scale (BARS)	Safety Set
	14.3.4.5.4	Summary of Children's Depression Rating Scale – Revised (CDRS-R) Raw Summary Score	Safety Set
	14.3.4.5.5	Summary of Pediatric Anxiety Rating Scale (PARS) Total Score	Safety Set
		Post-Hoc Analysis	
	14.3.4.6a	Shift from Baseline Summary: BMI z-score	Safety Set
	14.3.4.6b	Shift from Baseline Summary: Height z-score	Safety Set
	14.3.4.6c	Shift from Baseline Summary: Weight z-score	Safety Set
	14.3.4.7a	Shift from Baseline Summary: 12-Lead Electrocardiogram QTC	Safety Set
	14.3.4.7b	12-Lead Electrocardiogram Outliers	Safety Set

Header	Table Number	Name	Analysis Set
	14.3.4.7c	Vital Sign: Heart Rate Outliers	Safety Set
	14.3.4.8	Shift from Baseline Summary: HbA1c	Safety Set
	14.3.4.9	Shift from Baseline Summary: Cholesterol	Safety Set

15. Index of Listings

Data collected in the database will be listed. Numbering of listings may be adjusted to accommodate split listings or listings that are omitted due to no records.

Header	Listing Number	Name	Analysis Set (Example)
16.2		Subject Data Listings	
	16.2.1.1	Subject Disposition	Enrolled Set
	16.2.1.2	Baseline Failure	Enrolled Set
16.2.2		Protocol Deviations	
	16.2.2.1	Protocol Deviations	Safety Set
	16.2.2.2	COVID-19 Study Disruptions	Enrolled Set
16.2.3		Subjects Excluded from the Efficacy Analysis	
	16.2.3.1	Analysis Population	Enrolled Set
	16.2.3.2	Inclusion/Exclusion Criteria	Enrolled Set
16.2.4		Demographic Data	
	16.2.4.1	Demographics and Baseline Characteristics	mITT Set
	16.2.4.1b	Demographics and Baseline Characteristics	ITT Set
	16.2.4.2	Medical History	Safety Set
	16.2.4.3	Psychiatric History	Safety Set
	16.2.4.4	Prior and Concomitant Medications	Safety Set
	16.2.5.1	Study Drug Administration	Safety Set
16.2.6		Individual Efficacy Response Data	
	16.2.6.1	Yale Global Tic Severity Scale (YGTSS)	mITT Set
	16.2.6.1b	Yale Global Tic Severity Scale (YGTSS)	ITT Set
	16.2.6.2	Clinical Global Impression of Tourette Syndrome (CGI-TS)	mITT Set
	16.2.6.2b	Clinical Global Impression of Tourette Syndrome (CGI-TS)	ITT Set
	16.2.6.3	Gilles de la Tourette Syndrome –Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL)	mITT Set
	16.2.6.3b	Gilles de la Tourette Syndrome –Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL)	ITT Set
16.2.7		Adverse Event Listings	
*	16.2.7.1	Adverse Events	Safety Set
	16.2.7.2	Serious Adverse Events	Safety Set
	16.2.7.3	Adverse Events Leading to Study Termination	Safety Set
	16.2.7.4	Adverse Events Leading to Death	Safety Set
	16.2.7.5	Adverse Events of Special Interest for Parkinsonism	Safety Set

Header	Listing Number	Name	Analysis Set (Example)
	16.2.7.6	Adverse Events of Special Interest for Ecopipam	Safety Set
16.2.8		Listing of individual laboratory measurements by patient	
	16.2.8.1	Clinical Laboratory Data	
	16.2.8.1.1	Hematology Laboratory Evaluations	Safety Set
	16.2.8.1.2	Biochemistry Laboratory Evaluations	Safety Set
	16.2.8.1.3	Urinalysis Laboratory Evaluations	Safety Set
	16.2.8.1.4	HbA1c Laboratory Evaluations	Safety Set
		Other Safety Data	
	16.2.8.2	Vital Signs	Safety Set
	16.2.8.3	12-Lead Electrocardiogram	Safety Set
	16.2.8.4	Physical Examination	Safety Set
	16.2.8.5.1	Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Ideation	Safety Set
	16.2.8.5.2	Columbia-Suicide Severity Rating Scale (C-SSRS) – Intensity of Ideation	Safety Set
	16.2.8.5.3	Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Behavior	Safety Set
	16.2.8.5.4	Columbia-Suicide Severity Rating Scale (C-SSRS) – Actual Attempts	Safety Set
	16.2.8.6	Abnormal Involuntary Movement Scale (AIMS)	Safety Set
	16.2.8.7	Barnes Akathisia Rating Scale (BARS)	Safety Set
	16.2.8.8	Children's Depression Rating Scale Revised (CDRS-R)	Safety Set
	16.2.8.9	Pediatric Anxiety Rating Scale (PARS)	Safety Set
	16.2.9.1	Height, Weight and BMI Z-Scores	Safety Set

16. Index of Figures

Header	Figure Number	Name	Analysis Set (Example)
14.2	14.2.1.4.1a	Mean (+/- SD) C&A-GTS-QOL Change from Baseline Total Score Over Time	mITT Set
	14.2.1.4.1b	Mean (+/- SD) VAS Change from Baseline Score Over Time	mITT Set
14.3	14.3.4.6a	Mean (+/- SD) BMI z-Score Over Time	Safety Set
	14.3.4.6b	Mean (+/- SD) Height z-Score Over Time	Safety Set
	14.3.4.6c	Mean (+/- SD) Weight z-Score Over Time	Safety Set

17. Appendices

17.1. Schedule of Assessments

Assessment4	**Baseline*** (Titration)	Treatment											**End of Study / Early Termination**	**Follow Up Visit**	**Follow Up Phone Call**
Study Month	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**One and TwoWeeks Post Last Dose**	**30 Days After Last Dose**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 & 15**	
Visit Window		±3days	±3days	±3days	±3days	±3days	±3days	±3days	±3days	±3days	±3days	±3days	±3days	±3days	±3days
Informed Consent	X														
Inclusion/ Exclusion	X														
Medical/Psychiatric/ medication History	X														
Physical Examination	X	X		X			X			X			X	X	
Vital Signs1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X	X		X			X			X			X		
Laboratory Tests (Hematology and Chemistry)2	X	X		X			X			X			X	X	
Urine Drug Screen	X	X		X			X			X			X		
Urine Pregnancy Test	X	X		X			X			X			X		

Assessment4	**Baseline*** (Titration)	Treatment											**End of Study / Early Termination**	**Follow Up Visit**	**Follow Up Phone Call**
Study Month	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**One and TwoWeeks Post Last Dose**	**30 Days After Last Dose**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 & 15**	
HbA1c		X		X			X			X			X		
YGTSS Score	X	X		X			X			X			X		
CGI-TS-I		X		X			X			X			X		
CGI-TS-S	X	X		X			X			X			X		
C&A-GTS-QOL	X	X		X			X			X			X		
Columbia Suicide Severity Rating Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Abnormal Involuntary Movement Scale (AIMS)	X	X	X	X	X	X	X	X	X	X	X	X	X		
Barnes Akathisia Ratings Scale (BARS)	X	X	X	X	X	X	X	X	X	X	X	X	X		
Children's Depression Rating Scale-Revised (CDRS-R)	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pediatric Anxiety Ratings Scale (PARS)	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment4	**Baseline*** (Titration)	Treatment											**End of Study / Early Termination**	**Follow Up Visit**	**Follow Up Phone Call**
Study Month	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**One and TwoWeeks Post Last Dose**	**30 Days After Last Dose**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 & 15**	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X3		
Collect Unused Study Drug/Assess Drug Compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: BP = blood pressure, CGI = Clinician Global Impression, CGI-TS-I = CGI Tourette Syndrome of Improvement, CGI-TS-S = CGI Tourette Syndrome of Severity, ECG = electrocardiogram, HbA1c = Hemoglobin A1c

* Baseline is to occur within 30 days of the EBS-101-CL-001 14 Day Follow Up Visit (or longer with the permission of the medical monitor). All Baseline measurements can be taken from the Day 14 Follow Up Visit of the EBS-101-CL-001 study if performed less than 7 days prior to the Baseline visit. In this case, the HbA1c and Urine Drug Screen from the Week 12/Completion Visit of the EBS-101-CL-001 study may be used.

1 Vital signs will include heart rate, BP, orthostatic BP and heart rate (done supine and then 3 minutes after standing), height and weight.

2 Subjects should be in a fasting state (8 hours) for laboratory tests.

3 Study drug dispensation for down titration.

4 Assessments for Study Visits may be completed in locations other than study clinic and/or safety and efficacy assessments required at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event.

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