ECOPIPAM (EBS-101)
EBS-101-TD-301

IND Number:	109746
EU CT Number:	2023-503494-38-00
EudraCT Number:	2022-001961-11
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
Public Title:	Ecopipam Tablets to Study Tourette's Disorder in Children, Adolescents and Adults
Indication Studied:	Children, Adolescent and Adult Subjects with Tourette's Disorder
Protocol Version/Date:	9.0, 05 March 2024
Sponsor Address:	Emalex Biosciences, Inc. 330 North Wabash Avenue, Suite 3500 Chicago, IL 60611

The program will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Confidentiality Statement

The information in this document contains trade and commercial information that is privileged or confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential.

SUMMARY OF SIGNIFICANT CHANGES

SIGNIFICANT PROTOCOL CHANGES V8.0 to V9.0	RATIONALE
Updated schedule of assessments to emphasize neurological exam as part of physical exam at the Week 4/Day 29 visit and to allow for laboratory assessment if serotonin syndrome symptoms are present.	Updated to include the assessment of serotonin syndrome per request from FDA.
Updated schedule of assessments to delete the need for blood pressure measurements to be performed prior to ECG.	Allow flexibility in the way the assessments are performed.
Hydroxyzine removed from prohibited medication list (Section 23 and Section 24).	To corr ct hydroxyzine being listed both as prohibited and allowed medication.

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Emalex Biosciences, Inc. This program will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization (ICH) Tripartite: Harmonized Guideline for Good Clinical Practice E6.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.

Responsible Medical Officer:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 05-Mar-2024 | 14:17 PST
8CF498D19E72409EABBA8B68F9C7900B

05-Mar-2024 | 14:17 PST

[redacted]
Emalex Biosciences, Inc.

Date

Clinical Study Leader:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 05-Mar-2024 | 16:26 PST
36AEB882D5204AD18D779FC6ED4C8191

05-Mar-2024 | 16:26 PST

[redacted], Clinical Operations
Emalex Biosciences, Inc.

Date

INVESTIGATOR'S AGREEMENT

I have read the protocol EBS-101-TD-301 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Clinical Study Leader	[redacted]	[redacted]
Drug Safety Physician	Syneos Medical Physician	+1 (877) 462-0134
24-Hour emergency contact	Syneos Medical Physician	+1 (877) 462-0134

2. SYNOPSIS

Name of Sponsor/Company: Emalex Biosciences, Inc.	
Name of Investigational Product: Ecopipam Tablets	
Protocol Number: EBS-101-TD-301	
Title of Study: 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	
Study centers: Approximately 90 sites	
Studied period (years): Estimated date first subject enrolled: 1Q 2023 Estimated date last subject completed: 3Q 2024	**Phase of development:** 3
Objectives: Primary: 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). Secondary: 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 to <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. Exploratory: To evaluate the population PK/pharmacodynamic (PD) relationships with ecopipam during the open-label Stabilization period of the study.	
Methodology: 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 children/adolescent caregivers) and assent (children/adolescents) and following an up to 28-day Screening period and completion of 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 (2 mg/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 after Baseline. 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 assessments will be conducted at Weeks 4 and 8. A PK assessment may be conducted at	

Week 12 if the Week 8 PK assessment is missed. Safety assessments will be conducted at all visits including the telephone visit at Week 2.

Responders to ecopipam, defined as those with ≥ 25% improvement from Baseline on the YGTSS-TTS (Yale Global Tic Severity Scale-; Total Tic Score) 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).

Non-responders to ecopipam during the open-label Stabilization p riod at either Week 8 or Week 12, Responders to ecopipam who complete the R/WD period, any subject who meets Relapse criteria during the R/WD period, and any subject who discontinues the study prematurely due to 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 who do not roll into the open-label ext nsion study EBS-101-TD-391 will also be contacted by telephone 30 days after the last dose of s udy medication to determine any adverse events.

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 the long-term open-label study EBS-101-TD-391. Subjects who meet he 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.

In anticipation of reaching the target number of Relapse events, randomization into the double-blind R/WD period may be closed, at which time subjects in the open-label Stabilization period may continue in the study until the Week 12 visit. Upon completion of the Week 12 visit, subjects will have the opportunity to enter 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 enter the open-label study EBS-101-TD-391.

Number of subjects (planned): The minimum number of subjects enrolled will be based on the number of Relapses in the combined children and adolescent groups (age ≥ 6 to < 18 years of age). Subject enrollment will stop around the time that 49 Relapse events are anticipated to occur among these subjects. The number of Relapses among adults will not determine number of subjects enrolled in the study.

Assuming the proportions of child and adolescent subjects who Relapse in the R/WD period are 65% in the placebo group and 34% in the ecopipam group, approximately 98 subjects (~49 subjects per treatment group) may need to be Randomized to achieve this number of Relapse events.

Assuming a Response rate of 50%, approximately 196 subjects age ≥ 6 to < 18 years of age would need to enter the open-label Stabilization period to randomize 98 subjects aged ≥ 6 to < 18 years.

Adult subjects with TD who meet all inclusion criteria and none of the exclusion criteria are eligible to enroll in the study, and approximately 40 adult subjects are estimated to enroll.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. If <18 years of age, subject's parent or legal guardian must sign a written informed consent and subject must sign a written informed assent according to the requirements of the site's IRB/EC. If ≥18 years of age, subject must sign a written informed consent according to the requirements of the site's IRB/EC.
2. Subjects must be ≥ 6 years of age at time of screening.
3. Subjects must weigh at least ≥18 kg (39.6 lbs).
4. Subjects must have TD based on the Diagnostic and Statistical Manual for Mental Disorders – 5th Edition-Text Revision (DSM-5-TR) diagnostic criteria for TD.
5. Subjects must exhibit both motor and vocal tics that cause impairment with normal routines.
6. Subjects must have a minimum s ore of 20 on the YGTSS-TTS at Screening and at Baseline visits with tic symptoms causing impairment in the subject's normal routines, including academic achievement, and/or occupational functioning, and/or social activities, and/or relationships or wh se symptoms distress the subject to the extent that treatment is appropriate.
7. Female participants of childbearing potential must agree to use a highly effective method of contraception (i.e., pregnancy rate of less than 1% per year) during the study and for 30 days after the discontinuation of the IMP. Adequate contraceptive methods include combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception with inhibition of ovulation (oral, injectable, implantable), intrauterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal occlusion, vasectomized male partner or a female participant who is not of childbearing potential.

   Female participants and female partners of male study participants using a hormonal contraceptive must also use a barrier method (i.e., condom or occlusive cap [diaphragm or cervical/vault caps]) and should have been stable on their hormonal contraceptive treatment for at least 4 weeks prior to Screening.
8. Sexually active male subjects must use a highly effective method of contraception during the study and agree to continue the use of highly effective contraception for at least 30 days after the last dose of study drug.

9. For sites in the EU only, the subject must have received an adequate trial of non-pharmacological therapy without adequate response prior to study enrollment.

Exclusion Criteria:

1. Subjects with previous exposure to ecopipam (e.g., participated in study PSY301, PSY302 or EBS-101-CL-001).
2. Subjects with any unstable mood disorder (DSM-5-TR criteria) at Screening or Baseline.
3. Subjects who have unstable medical illness or clinically significant abnormalities on laboratory tests, or ECG at Screening as determined by the Principal Investigator.
4. Subjects with a significant risk of attempting suicide based on history (suicide attempt in past 1 year or who have had 2 or more lifetime suicide attempts) or who had an answer of ''yes'' on any question other than 1–3 (currently or within the past 30 days) on the baseline/screening version of the Columbia Suicide Severity Rating Scale (C-SSRS).
5. Subjects with a clinical presentation at Screening or Baseline and/or history consistent with another neurologic condition that may have had accompanying abnormal movements (e.g., Huntington's disease, Parkinson's disease, Wilson's disease, stroke, Restless Legs Syndrome).
6. Female subjects who are currently pregnant or lactating or planning to become pregnant during the study.
7. Subjects who have moderate to severe renal impairment.
8. Subjects who have hepatic impairment at Screening.
9. Subjects with current or recent (past 3 months) history of DSM-5-TR substance use disorder (except for nicotine).
10. Subjects with positive urine drug screen for cocaine, amphetamine, benzodiazepines, barbiturates, phencyclidine (PCP), or opiates at Screening, except those receiving stable, prescribed treatment for attention deficit/hyperactivity disorder (ADHD).
11. Subjects with a ≥25% difference in the absolute change in YGTSS-TTS between the Screening visit and the Baseline visit.
12. Subjects with a lifetime history of bipolar disorder type I or II, dementia, schizophrenia, or any other psychotic disorder
13. Subjects with an on et of a maj r depressive episode in the past 6 months.
14. Subjects with a PHQ-9 score ≥10 at Screening or Baseline.
15. Subjects with a history of seizures (excluding febrile seizures that occurred >2 years prior to Screening).
16. Subjects with a history of neuroleptic malignant syndrome.
17. Subjects with a myocardial infarction within 6 months prior to Screening.
18. Subjects who have had previous treatment with:
    - investigational medication within 4 weeks prior to Screening
    - oral neuroleptics within 4 weeks prior to Screening
    - depot neuroleptics within 3 months prior to Screening (e.g., risperidone microspheres) or 6 months prior to screening (e.g., paliperidone palmitate)
19. Subjects receiving any other medication to treat motor or vocal tics for at least 14 days prior to Baseline.
20. Subjects receiving unstable doses or excluded medications to treat depression, anxiety or ADHD during the 4 weeks prior to Screening.
21. Subjects who have a need for medications which would have unfavorable interactions with ecopipam, e.g., CYP2D6, CYP3A4, CYP2C19, P-gp, substrates with a narrow therapeutic window (e.g., digoxin), inhibitors of CYP2D6 (e.g., fluoxetine), broad-spectrum UGT enzyme inhibitors (e.g., valproic acid), dopamine antagonists (e.g., neuroleptics) or agonists

(including bupropion), tetrabenazine, VMAT-2 inhibiters (e.g. tetrabenazine), tricyclics and tetracyclics, monoamine oxidase inhibitors, or St. John's Wort. See Section 23.

22. Subjects who have initiated new psychological therapies or deep brain stimulation within 10 weeks prior to Baseline visit.
23. Initiation or changes in psychological therapies during the study (i.e., Habit Reversal Training or Comprehensive Behavioral Intervention for Tics) as well as deep brain stimulation.
24. Subjects unable to swallow tablets.
25. Subjects with a known hypersensitivity to any excipients of ecopipam tablets, including subjects with confirmed lactose intolerance.
26. Subjects who are employed by the sponsor, vendors working on the study, study site personnel or their family members.
27. Siblings or family members of any current subject participating in the study.
28. Subjects deprived of liberty by administrative or judicial decision, patients under court protection, guardianship, curatorship or family guardianship.
29. Any subject who in the opinion of the investigator is not a suitable candidate for the study.

Investigational product, dosage and mode of administration:

Ecopipam 11.2-, 22.4-, 33.6-, 44.8-, 67.2- and 89.6-mg tablets containing 12.5-, 25-, 37.5-, 50-, 75- and 100-mg ecopipam HCl respectively; 1.8 mg/kg/day ecopipam (2 mg/kg/day ecopipam HCl) target dose; oral administration.

Dosing will be stratified by the following weight bands to better achieve the 1.8 mg/kg/day ecopipam (2 mg/kg/day ecopipam HCl) target dose: ≥18 - ≤23 kg, >23 - ≤34 kg, >34 - ≤44 kg, >44 - ≤68 kg, >68 - ≤83 kg, > 83 kg. Dosing will be based on the subject's weight at the Baseline and will not be adjusted if the subject's weight changes at subsequent visits.

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

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	150
>83	22.4	25	44.8	50	89.6	100	179.2	200

During the 8-week maintenance phase of the Stabilization period and for those randomized to ecopipam in the R/WD period, the following ecopipam doses (or matching placebo for those randomized to placebo during the R/WD period) 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 once daily in the evening without regard to meals.

Non-responders to ecopipam during the open-label Stabilization period, subjects randomized to placebo during the R/WD period, responders to ecopipam who complete the R/WD period, any subject who meets Relapse criteria during the R/WD period, and any subject who discontinues the study prematurely due to any reason will be tapered off ecopipam in decrements of 22.4 mg/day (25 mg ecopipam HCl) until off drug; signs or symptoms of wi hdrawal, abuse and dependence will be monitored. Subjects assigned to placebo will receive placebo taper down medication to preserve the blind.

Duration of treatment:

Eligible subjects will receive open-label ecopipam tablets for up to 12 weeks. Subjects who qualify as Responders will be randomized at Week 12 to receive either ecopipam tablets or matching placebo for up to 12 weeks for a total of up to 24 weeks of treatment.

Reference therapy, dosage, and mode of administration:

Placebo-controlled, matching placebo tabl ts given by mouth (PO) in the evening.

Criteria for evaluation:

Efficacy:

Primary Efficacy Endpoint:

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

Secondary Efficacy Endpoint:

- 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.

Exploratory Efficacy Endpoints:

- 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. 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.
- 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. 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.

- Mean change from Randomization (Week 12) to Week 24 in the YGTSS-TTS for ecopipam compared to placebo.
- Mean change from Randomization (Week 12) to Week 24 in the Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) for ecopipam compared to placebo.
- Mean change from Randomization (Week 12) to Week 24 in the YGTSS-Global Severity (GS) score for ecopipam compared to placebo.
- Mean change from Randomization (Week 12) to Week 24 in the Caregiver Global Impression of Change (CaGI-C) for ecopipam compared to placebo.
- Time from Randomization (Week 12) to a loss of ≥ 50% of the improvement from Baseline (Day 1) experienced on the Yale Global Tic Severity Scale- Total Tic Score (YGTSS-TTS) at the last visit (Week 12) in the open-label Stabilization period.
- 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.
- Mean change from Randomization (Week 12) to Week 24 in the Premonitory Urge for Tics Scale (PUTS) for ecopipam compared to placebo.
- Mean change from Baseline (Day 1) to Week 24 in Gill s de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) score for ecopipam compared to placebo.
- Mean change from Baseline (Day 1) to Week 24 in Gilles de la Tourette Syndrome–Quality of Life Scale (GTS-QOL) score in adults f r ecopipam compared to placebo.
- Mean change from Baseline (Day 1) to Week 12 in the YGTSS-TTS.
- 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.
- Mean change from Baseline (D y 1) to Week 24 in the YGTSS-TTS for ecopipam compared to placebo.
- Mean change from Baselin (Day 1) to Week 24 in the YGTSS-GS score for ecopipam compared to placebo
- 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.
- Caregiver Global Impression of Change (CaGI-C) through Week 24 for ecopipam compared to placebo.
- 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.
- Mean change from Baseline (Day 1) to Week 24 in the Clinical Global Impression of Tourette Syndrome Improvement (CGI-TS-I) for ecopipam compared to placebo.
- Time from Randomization (Week 12) to treatment discontinuation during the double-blind R/WD period for ecopipam compared to placebo.
- Time from Randomization (Week 12) to loss of ≥ 100% of the improvement experienced on the Yale Global Tic Severity Scale- Total Tic Score (YGTSS-TTS) from Baseline (Day 1) to the last visit (Week 12) in the open-label Stabilization period for ecopipam compared to placebo.
- To evaluate the population PK/pharmacodynamic (PD) relationships with ecopipam during the open-label Stabilization period of the study.

Additional analyses will include efficacy endpoints listed above at all earlier timepoints, and the YGTSS subscales individually (Motor, Vocal, and Impairment). The correlation between subjects meeting Relapse criteria based on YGTSS-TTS and those who also had at least a 1-point reduction on CGI-TS-S will also be investigated. If there is a strong correlation between subjects ≥6 and <18 years who meet Relapse criteria based on the YGTSS-TTS and have a worsening by at least one category of the CGI-TS-S, Relapse will not be a competing risk, and therefore the time to worsening of the CGI-TS-S for subjects ≥6 and <18 years will be considered a secondary endpoint. Similarly, if there is a strong correlation between all subjects irrespective of age who meet Relapse criteria based on the YGTSS-TTS and have a worsening by at least one category of the CGI-TS-S, Relapse will not be a competing risk, and therefore the time to worsening of the CGI-TS-S for all subjects irrespective of age will be considered a secondary endpoint.

Subgroup analyses will also be conducted on all efficacy endpoints listed above for the following populations:

- Children (≥ 6 and < 12 years of age), Adolescents (≥ 12 and < 18 years of age), and Adults (≥ 18 years of age).
- Subjects per region
- 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)

Rank order of hierarchy of the secondary and exploratory endpoints will be outlined in the statistical analysis plan.

Safety:

Safety will be assessed by monitor ng and recording all adverse events (AEs) and Serious Adverse Events (SAEs) at all Visits, regular monitoring of hematology, blood chemistry, urinalysis and prolactin (Screening, Basel n Weeks 12 and 18, Completion [Week 24] or Relapse/Early Termination, and 7- and 14-day Follow Up visits). HbA1c will be measured at Baseline, Week 12 and Completion Week 24 visits. Regular measurement of vital signs and the performance of a physical examination will occur at every visit. An ECG will be done at Screening, Baseline and Weeks 4, 12, 18, and 24 and at the 7-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). Additional safety outcomes (occurring at specified visits at 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) for children and adolescents, the Pediatric Anxiety Rating Scale (PARS), for children and adolescents, the Swanson, Nolan and Pelham (SNAP-IV-26) questionnaire for children and adolescents, the Children's Yale-Brown Obsessive-Compulsive Scale-II (CY-BOCS-II), the Conners Adult ADHD Rating Scale – Self Report:Short Version (CAARS-S:S) for adults, the Hamilton Rating Scale for Anxiety (HAM-A) for adults, the Patient Health Questionnaire-9 (PHQ-9) for adults, the Yale-Brown Obsessive-Compulsive Scale-II (Y-BOCS-II) for adults, and the Extrapyramidal Symptom Rating Scale (ESRS) for children, adolescents, and adults.

PK:

Blood samples will be collected to measure concentrations of ecopipam and its major (active) metabolites at Weeks 4 and 8. If the Week 8 PK assessment is missed, samples may be drawn at Week 12 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).

Statistical methods:

Efficacy:

Sample Size Justification:

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 for 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 double-blind R/WD 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 anticipated to be enrolled.

Interim Analysis:

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). Full details will be provided in the Statistical Analysis Plan (SAP).

Analysis Population and Methods:

The Modified Intention-to-Treat (mITT) population will include all randomized subjects who received at least one dose of study drug post randomization. The mITT population will be used for the analysis of the efficacy endpoints.

The primary efficacy endpoint for this trial is Time from Randomization (Week 12) to Relapse in subjects ≥ 6 and < 18 years during the double-blind R/WD period defined as a loss of ≥ 50% 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, or initiation of additional medications to treat symptoms of TD; or requirement of hospitalization for worsening symptoms of TD. 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 secondary endpoint will be evaluated in a similar manner as the primary efficacy endpoint. Details will be provided in the SAP.

The Per-Protocol (PP) population will include subjects from the mITT population 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 to identify protocol deviations that may potentially affect the results. At this time, it will be determined if subjects and/or data should be excluded from the PP Population. The list of subjects or observations to be excluded from the PP Population, 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.

Efficacy endpoints will be tested using a rank order hierarchy to preserve alpha. Full details will be specified in a formal SAP.

Safety:

The safety population will include all enrolled subjects who received at least one dose of study drug. The safety population will be used for the analysis of the safety endpoints.

PK:

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.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol:

Abbreviations	Terms
ADD	Attention Deficit Disorder
ADHD	attention deficit/hyperactivity disorder
ADL	Activities of Daily Living
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AMP	adenosine monophosphate
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
AUC	area under the plasma-concentration time course profile
$AUC_{(0\text{-}24\ hr)}$	area under the plasma-concentration time course profile from time 0 (dosing) to 24 hours after dosing
BUN	blood urea nitrogen
C&A-GTS-QOL	Child and Adole cent Gilles de la Tourette Syndrome-Quality of Life Scales
CAARS-S:S	Conners Adult ADHD Ratings Scale – Self Report: Short Version
CaGI-C	Car giver Global Impression of Change
CFR	Code of Federal Regulations
CDI	Children's Depression Inventory
CDRS-R	Children's Depression Rating Scale-Revised
CY-BOCS-II	Children's Yale-Brown Obsessive-Compulsive Scale-II
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
C_{max}	maximum observed concentration
CNS	Central nervous system
COVID-19	SARS-CoV-2 (coronavirus)
CRA	Clinical research associate
CRO	Clinical research organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCI	Diagnostic Confidence Index
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition-Text Revision

DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EEG	Electroencephalogram
ESRS	Extrapyramidal Symptom Rating Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GS	Global score
GTS-QOL	Gilles de la Tourette Syndrome–Quality of Life Scale
HAM-A	Hamilton Rating Scale for Anxiety
HCl	Hydrochloride
123I-β-CIT SPECT	(2β-carbomethoxy-3β-[4-iodophenyl]tropane) single photon emission computed tomography
HbA1c	Hemoglobin A1c
IA	Interim analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IMP	Investigational medicinal product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
Ki	Inhibition constant
LDH	lacta e dehydrogenase
LFT	Liv r function test(s)
LND	Lesch Nyhan Disease
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OCD	Obsessive-Compulsive Disorder
PARS	Pediatric Anxiety Rating Scale
PCP	Phencyclidine
PET	Positron emission tomography
PHQ-9	Patient Health Questionnaire – 9
PI	Principal Investigator
PO	Oral (per os)
PUTS	Premonitory Urge for Tics Scale
QD	Once daily
SAE	serious adverse event
SC	Subcutaneous
SCH	Schering-Plough drug code indicator
SNAP-IV-26	Swanson, Nolan, and Pelham-IV-26 questionnaire
t_{max}	time from dosing to the maximum observed concentration
TD	Tourette's Disorder
THC	Tetrahydrocannabinol
TS	Tourette's Syndrome

TTS	Total Tic Score
US	United States
WMA	World Medical Association
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

5. INTRODUCTION

5.1. Background on Tourette's Disorder

Tourette's Disorder (TD) is a neurological disorder characterized by motor or vocal tics that begin in childhood and persist over time (see box below with the Diagnostic and Statistical Manual for Mental Disorders – 5th Edition DSM-5-TR diagnostic criteria[18]). The tics are brief in duration, occur spontaneously, and do not show a regular temporal pattern. Further, the tics are not caused by medications, other medical reasons, or confirmed neurological abnormality. They can be consciously suppressed for some time and are exacerbated by stress. Males are more susceptible than females with a ratio of about 4.3 to 1. Motor tics can include such things as eye-blinking, facial grimacing, mouth movements, head jerks, shoulder shrugs and arm/leg jerks. In more severe cases gyrating, bending, pivoting and dystonic movements are possible. Vocal tics are fast meaningless sounds or noises, and include such things as sniffing, throat clearing, grunting, barks and squealing. Complex vocal tics can include shouting out of single words, whole sentences or repeating words (echolalia). In small numbers of subjects, explosive obscenities (coprolalia) are possible.[1,2] Diagnosis of TD is complicated because it often co-exists with other psychiatric illnesses. Common co-morbid conditions include attention deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, and depression.[2] These symptoms often mask TD and make diagnosis difficult. Tic severity can range from mild to severe according to its frequen y and intensity.

DSM-5-TR Diagnostic Criteria for Tourette's Disorder

Note: A *tic* is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization.

A. Both multiple motor and one or more v cal tics have been present at some time during the illness, although not necessarily concurrently.

B. The tics may wax and wane i frequency but have persisted for more than 1 year since first tic onset.

C. The onset is before age 18 years.

D. The disturbance is not attributable to the physiological effects of a substance (e.g., Cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).

Natural History of Tics

The tics have a variable course, with severe bouts interspersed with complete absence of symptoms. Onset of tics is seen early in childhood (average approximately 7 years) and peaks in the teenage years. Vocal tics appears several years after the onset of motor tics. For most subjects, the period of worst-ever tic severity is between 7 and 15 years of age, followed by a steady decline in tic severity. As subjects mature, the vast majority of tics will disappear permanently, with a small percentage of subjects having tics that persist into adulthood and require treatment. Complete remission of tics is reported in approximately 50% of subjects. Severe tics are thought to occur only in about 10% of the cases.[3] Approaches to the treatment of

tics include education, behavioral therapy, pharmacological therapy, and treatment of comorbid conditions (ADHD, OCD). Approximately, 20% of subjects do not need treatment. Counseling and behavioral therapy may be sufficient with mild symptoms. Medications should be considered when tics interfere with peer relationships, social interactions, job or school performance or interfere with activities of daily living. Medications should be started at low doses, titrated up slowly to lowest effective dose and tapered slowly during non-stressful periods. Medication therapy incudes: dopamine receptor blocking agents, dopamine depleting agents, alpha agonists, noradrenergic agents, benzodiazepines, low dose dopamine agonists, botulinum toxin and neurosurgical treatment. Non-selective dopamine receptor blocking agents have been the mainstay of treatment and are the most effective. They suppress tics in 70-80% of subjects. Many subjects eventually discontinue medication therapy due to adverse events, including extra-pyramidal disorders, somnolence, blood glucose changes, weight gain, and effects on lipids. A selective dopamine-1 (D1) receptor antagonist may mitigate against some of these adverse events and has the potential to offer a safer alternative option.

5.1.1. Disrupted Dopamine Systems in Tourette's Disorder

The underlying mechanism responsible for TD is unknown. Although the disease tends to run in families, there have been no definitive genetic mutations identified.[4] Research to date has indicated that dopamine circuits in the central nervous system (CNS) are intimately involved based on the following observations:[5,6,7]

- Dopamine-rich areas of the brain (e g., striatum) are believed to control motor tics
- Clinical neuroimaging studies of TD subjects implicate dopamine-rich brain areas
- Dopamine antagonists can ameliorate tics
- Catecholamine depletors (e.g., tetrabenazine) can ameliorate tics

5.2. Background on Ecopipam

5.2.1. Nonclinical Data

5.2.1.1. Toxicology

The nonclinical development program for ecopipam comprised studies of bioavailability, acute and repeated-dose toxicity (including juvenile rats) oral and gavage [PO], intramuscular [IM], intravenous [IV], and subcutaneous [SC] routes of administration), cardiovascular; neurological, behavioral, and autonomic nervous system, reproductive and endocrinological, and genetic toxicity. Results from the extensive nonclinical studies demonstrate that ecopipam is well tolerated. Ecopipam did not cause any appreciable changes in cardiovascular function, any neurological disorders, or loss of efficacy/tolerance. Ecopipam HCl is not considered embryotoxic, fetotoxic, or teratogenic in rats at doses up to 162 mg/kg. In rabbits, the no-observable-effect level for both maternal and developmental toxicity is > 150 mg/kg, but < 300 mg/kg. Ecopipam is not considered genotoxic or mutagenic. However, ecopipam HCl was found to have a consistent sedative effect 2 hours after dosing in primates and to cause convulsions in mice, rats, and primates after high doses (>10 mg/kg). Ecopipam did not cause any movement disorders in mice, rats, or primates.

In a recently completed toxicology study, ecopipam HCl administered at doses of 6, 36, and 216 mg/kg/day orally to juvenile rats was well tolerated with no compound-related deaths and no adverse effects on sexual maturation, Functional Observational Battery testing, acoustic startle habituation, ophthalmologic examinations, estrous cycling, mating and fertility, ovarian and uterine examinations, clinical pathology, macroscopic pathology, or microscopic pathology. Administration resulted in clinical signs and reduction in body weight gains and body weights at ≥ 36 mg/kg/day and reductions in food consumption at 216 mg/kg/day. Spleen weights were reduced in the 216 mg/kg/day dose group at the end of the dose period; these findings were not observed at the end of the recovery period.

Results of nonclinical pharmacokinetic and metabolism studies showed that ecopipam is rapidly absorbed after oral dosing and, in rodents and monkeys, is metabolized to the N-desmethyl analog (N-desmethyl-ecopipam or EBS-101-40853). Both ecopipam and N-desmethyl-ecopipam are extensively conjugated. There are no qualitative differences in metabolic profiles of ecopipam between species. For rodents and nonhuman primates, the estimated oral bioavailability of ecopipam (parent drug) was very limited (0.6% in rats and 1.5% in monkeys).

Based on nonclinical hormonal and toxicology studies conducted with ecopipam, there is no evidence that ecopipam will have endocrinological effects in humans similar to that of the D2 antagonists.

Please refer to the Investigator's Brochure for m re detailed information about the known benefits and risks of ecopipam.

5.2.2. Clinical Data

Clinical Studies in Subjects with TD

With respect to TD, the following clinical studies support the use of ecopipam in patients with this disease:

Study PSY301

This was a Phase 2a, multicenter, non-randomized, open-label study of 44.8 mg ecopipam (50 mg ecopipam HCl) daily (Weeks 1–2) and then 89.6 mg (100 mg ecopipam HCl) daily (Weeks 3–8) in 18 adult subjects (≥ 18 to < 65 years of age) with TD. The primary efficacy end point was the change in the Yale Global Tic Severity Scale, Total Tic Score (YGTSS-TTS) from Baseline to Week 8.

Mean (SD) YGTSS-TTS was 30.6 (8.8) at Baseline and 25.3 (9.2) at 8 weeks (2-tailed paired $t17 = 4.4$; $p = 0.0004$). Mean (SD) YGTSS impairment score was 29.7 (10.9) at Baseline and 22.8 (13.7) at final visit ($t17 = 2.2$; $p = 0.04$).

There was no significant change in premonitory urges or psychiatric symptoms. Mean change in weight was −0.7 kg ($p = 0.07$). The most commonly reported adverse events were sedation (39%), fatigue (33%), insomnia (33%), somnolence (28%), anxiety (22%), headache (22%), and muscle twitching (22%).

Study PSY302

Study PSY301 was followed by a Phase 2, placebo-controlled, cross-over study of ecopipam in 40 children and adolescents with TD which further demonstrated that ecopipam treatment

decreases motor and phonic tics as assessed by the YGTSS-TTS in children and adolescents with TD. This study was a randomized, double-blind, placebo-controlled crossover study to evaluate the safety, tolerability, and efficacy of ecopipam in children and adolescents with TD. Forty pediatric patients (7-17 years of age) with TD and a total tic score of 20 on the YGTSS were randomized to ecopipam or placebo. The study consisted of an initial 30-day Treatment period (sequence 1), a 2-week Washout period, and a second 30-day Treatment period (sequence 2) where patients were crossed to the alternative treatment to which they were randomized.

The primary endpoint of the study was the change in YGTSS-TTS from Baseline to Day 30 for the ecopipam group compared to the placebo group. Method of analysis was based on the intention-to-treat (ITT) population with the last observation carried forward (LOCF). A simple analysis of variance (ANOVA) was prespecified as the primary statistical test. However, because of the numbers of subjects with unequal baseline visits, the assumptions of the ANOVA were violated, making it inappropriate to use. Therefore, the YGTSS-TTS was analyzed using a 2-way analysis of covariance (ANCOVA).

Reductions from BL in the YGTSS-TTS were significantly greater on ecopipam than placebo for the primary endpoint at Day 30 (-3.2; 95% CI, -0.3 to -6.1 P=0.033) and at an earlier timepoint at Day 16 (-3.7; 95% CI, -0.9 to -6.5 P=0.011). Significant reductions from BL in the YGTSS-Global Score (GS) were also observed at Day 30 and Day 16. There was also a significant change in the Clinical Global Impression of Severity (CGI-S) scales from Baseline to Day 30. The proportion of children and adolescents with moderate, marked, or severe symptoms decreased from 97.5% at baseline to 55% by Day 30 on ecopipam but remained at 80% by Day 30 on placebo.

Thirty-five subjects (87.5%) reported at least one AE during the study, with 149 AEs reported. The most frequently reported AEs (≥ 10% of subjects) in the ecopipam group were headache (15.0%), abdominal pain upper, insomnia, nausea, somnolence, and vomiting (each 10.0%). The most frequently reported AEs (≥ 10% of subjects) in the placebo group were headache (12.5%), nasopharyngitis (12.5%), and abdominal pain upper (10.0%). Most AEs (96.6%) were assessed by the investigator as mild or moderate in severity.

Twenty subjects (50.0%) reported a study drug-related AE while taking ecopipam and 10 subjects (25.0%) reported a study drug-related AE while taking placebo. The most frequently reported AEs (≥ 7.5%) considered related to study drug in subjects taking ecopipam were nausea (10.0%), somnolence (10.0%), abdominal pain upper, decreased appetite, fatigue, headache, and sedation (all 7.5%).

There were no deaths in the study. One subject (2.5%) prematurely discontinued from the study due to an AE of rash. One subject (2.5%) experienced a serious AE (SAE) of psychotic disorder approximately 55 days after the last dose of ecopipam. One subject (2.5%) required a dose reduction due to an AE of fatigue.

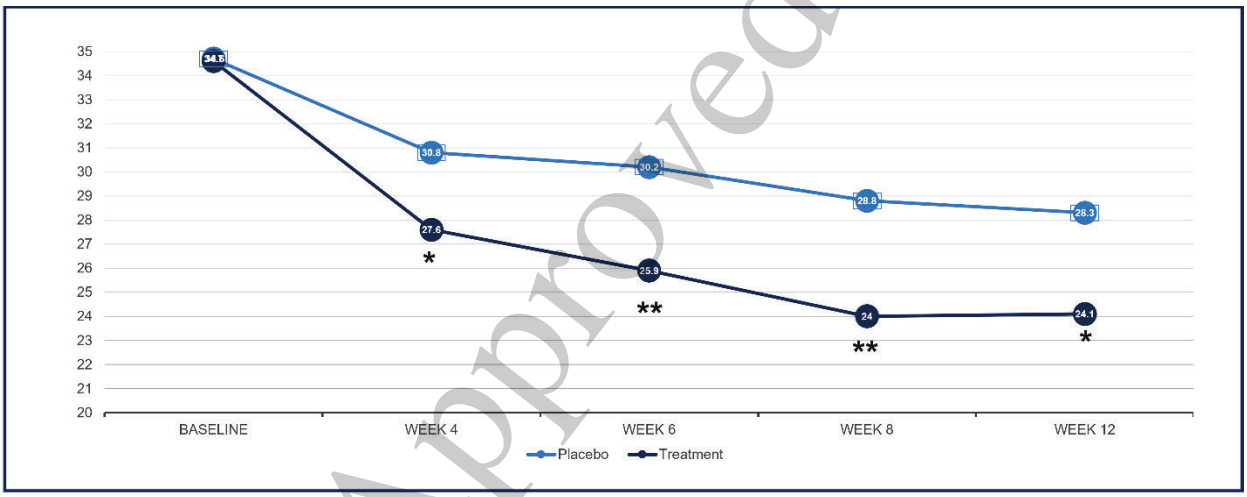
Two subjects (5.0%) reported suicidal ideation in the C-SSRS during the treatment phase. Overall, the data suggest that administration of ecopipam did not affect body weight. CDI scores, or S-SSRS scores compared with placebo. No clinically significant abnormalities in clinical laboratory evaluations, vital signs, ECG findings, or physical examination findings were observed following ecopipam administration.

Study EBS-101-CL-001

Based on the promising results of the Phase 2 clinical studies described above, Emalex initiated a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of ecopipam in 153 children and adolescents with TD (ages ≥ 6 to < 18). The study was conducted at 68 sites activated across the U.S., Canada, and Europe. Patients were randomized to receive either ecopipam tablets at a dose of 1.8 mg/kg/day (2 mg/kg/day ecopipam HCl) or placebo tablets. Study medication was titrated to the target dose over four weeks and then maintained for an eight-week treatment period.

The primary efficacy endpoint was the change from Baseline to Week 12 in the YGTSS-TTS. Statistically significant and clinically meaningful results were obtained on this primary endpoint at Week12, and significant differences to placebo were found at Weeks 4, 6 and 8 as well.

Figure 1: YGTSS-TTS: Baseline to End of Therapy for the mITT Population in Study EBS-101-CL-001



Week 4 p value = 0.02
Week 6 and Week 8 p values = <0.001
Week 12 p value = 0.011

The key secondary endpoint, the Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S), was also statistically significant at all timepoints from Week 6 to Week 12. In addition, other secondary endpoints were also significant including the YGTSS-Global Severity score (YGTSS-GS) and the Caregiver Global Impression of Change (CaGI-C). Two secondary endpoints, Clinical Global Impression of Tourette Syndrome Improvement (CGI-TS-I) and a patient rated quality of life instrument, were not statistically significant, although positive trends were observed on the CGI-TS-I, with significant results at earlier timepoints.

A summary of the primary and secondary efficacy data is presented in Table 2 below.

Table 2: Protocol EBS-101-CL-001 Efficacy Results (mITT Data set, MMRM analysis with imputation)

	Abbreviation	Placebo (n=74)	Ecopipam (n=75)	P value
Outcome Measures: mITT data set				
Primary Outcome: Yale Global Tic Severity Scale-Total Tic Score (motor + phonic tic scales) Baseline to week 12	YGTSS-TTS	-6.42	-9.87	0.011
Key Secondary Outcome: Clinical Global Impression of Tourette Syndrome – Severity Baseline to 12 weeks	CGI-TS-S	-0.53	-0.91	0.027
Predefined Hierarchy of Secondary Outcomes:				
Clinical Global Impression of Tourette Syndrome of Improvement Baseline to week 12	CGI-TS-I	3.42	3.04	0.079
Yale Global Tic Severity Scale -Global Severity score (motor + phonic + overall impairment scales) Baseline to week 12	YGTSS- GS	-13.56	-21.41	0.004
Caregiver Global Impression of Change At week 12	CaGI-C	3.55	2.49	0.007
Gilles de la Tourette Syndrome-Quality of Life Scale for Children and Adolescents Baseline to week 12	C&A-GTS-QOL	-8.81	-8.75	0.978
Subjects with a 25% improvement on the YGTSS-TTS At any time between baseline and 12 weeks		32 (43%)	53 (76%)	OR 3.67 P <0.001

The most frequent adverse events (≥ 5% and higher than placebo) were headache (15.8%), insomnia (9.2%), fatigue (7.9%), nasopharyngitis (6.6%), somnolence (7.9%), anxiety (5.3%), nausea (5.3%) and restlessness (5.3%). For less commonly reported adverse events, the same proportion of ecopipam- and placebo-treated patients reported suicidal ideation and depression. No deaths were reported in the study, 2 subjects treated with ecopipam and 1 subject treated with placebo experienced Serious AEs (SAEs), and 4 ecopipam-treated patients discontinued the study due to an adverse event. No metabolic events were observed and more patients on placebo gained weight than those who received ecopipam. No EPS-related events were observed and no difference from placebo was detected for other abnormal movement events. No clinically significant differences between ecopipam and placebo were noted in labs, vital signs, EKGs and in commonly used scales to detect anxiety, depression, suicidal ideation and behaviors, akathisia,

and tardive dyskinesia. Ecopipam did not adversely affect comorbid psychiatric conditions of ADHD.

In order to assess abuse potential of ecopipam in study EBS-101-CL-001, sites were instructed to assess for symptoms of drug abuse and withdrawal over the course of study medication treatment as well as during down-titration. Standardized Medical Queries (SMQs) based on MedDRA classification of preferred terms were conducted for abuse related AEs. The SMQ terms used were A) drug abuse and dependence and B) drug withdrawal. No symptoms or signs of either drug abuse/dependence or withdrawal were reported for subjects in the drug or placebo group. This, combined with data available from earlier studies, supports the reasoning that there is a low potential for ecopipam to cause drug abuse/dependence or withdrawal.

Study EBS-101-OL-001

Subjects who completed EBS-101-CL-001 as well as the 14 day follow up visit and who continued to meet the inclusion/exclusion criteria were eligible. Further, the Investigator had to determine that there was a potential benefit from continued participation. Of the 124 subjects who entered the study, 121 received at least one dose of ecopipam. The dose was adjusted to weight using the same weight bands designated for EBS-101-CL-001.

At study entry, baseline score of the YGTSS-TTS was an average of 29.6, which decreased to 17.3 at end of study. The CGI-TS-S score, the key secondary end point of the double-blind study, decreased from an average of 4.3 at baseline to 3.3 at six months, and 3.1 at month 12. The C&A-GTS-QoL Total Scores improved from a mean of 26.6 at baseline, to 18.7 at 6 months, and 19.0 at 12 months. The visual analog scale also improved over the trial. While open label studies can only inform efficacy these results support the durability of treatment effect of ecopipam in TD across multiple measures of disease severity and QoL.

A total of 80 subjects completed the study and 41 discontinued prematurely with 14 due to adverse events. Two subjects reported SAE: one possibly related to study drug (obsessive thoughts) and the other was se ondary to injuries suffered in a tornado and judged as not related to study drug. Ecopipam was not stopped in that case.

Treatment emergent adverse events (TEAEs) were reported in 84 subjects (69.4%) who received ecopipam. Forty of these events were considered by study investigators to be related to ecopipam. The most frequent TEAEs were nasopharyngitis (14%), anxiety (9.1%), insomnia (9.1%), abdominal Pain (8.3%), depression (8.3%), diarrhea (7.4%), headache (7.4%), somnolence (6.6%), pyrexia (5.8%), URI (5.8%), COVID-19 (5%), and nausea (5%). The most frequent treatment related adverse events were insomnia (8.3%), anxiety (6.6%). Depression (6.6%), and somnolence (5.8%). Two subjects (1.7%) reported suicidal ideation and 1 subject (0.83%) suicidal behavior. No adverse metabolic events were reported and z scores for BMI also showed no meaningful change.

A total of 14 subjects (11.6%) experienced AEs leading to treatment termination. The most commonly reported AEs leading to treatment termination (reported in ≥2 subjects) included anxiety and depression (2 subjects each, 1.7%). All other AEs leading to treatment termination occurred in 1 subject each.

With respect to potential AEs attributable to dopamine blockade, 2 subjects reported tremor and 1 subject each reported akathisia, balance disorder, bruxism, joint lock, and tongue biting.

Overall, neither reported AEs nor scores from systematic assessments for side effects revealed safety concerns for subjects treated with ecopipam.

5.3. Risk-Benefit Assessment

A consideration of the potential of risks that subjects with TD may be exposed to, approaches to reducing any such risks, and the possible benefits that they may derive from their participation in EBS-101-TD-301 is outlined below.

5.3.1. Assessment of Risk

A total of 193 children and adolescents (6 to 18) have been exposed to ecopipam, including 181 pediatric subjects with TD and 12 subjects with LND.

Ecopipam also been evaluated for safety in 2916 adult patients who participated in clinical trials for TD (N = 18) and other indications. A total of 1049 adult patients were treated with oral ecopipam for at least 180 days and 446 adult patients treated with oral ecopipam had at least 1 year of exposure.

As 2916 human subjects have been exposed to single and multiple doses of ecopipam and safety data including collection of adverse events, physical examinations, laboratory tests, ECGs, etc. have been systematically collected, there exists a fair body of information to base the understanding of potential risks and approaches to minimizing them in current and future studies.

The overall safety profile of ecopipam in clinic l studies have shown that the drug is generally well tolerated with the adverse events affecting primarily the CNS (e.g., headache, sedation, insomnia, psychiatric changes such as anxi ty, depression, and suicidal ideation) and the gastrointestinal system (e.g., nausea and vomiting).

In subjects with TD, ecopipam has been evaluated in five studies, one study in 18 adult subjects, one study in 40 children and adolesc nts with an open-label safety extension study, and one study in 141 children and adolesc nts with an open-label safety extension study.

There have been no deaths and 3 patients reported a total of 12 SAEs; one of anxiety (PSY-302A), one of psychotic disorder (PSY-302A), one of psychotic disorder (PSY-302) which occurred 55 days after last study dose, and one subject had 10 SAEs due to injuries suffered when his home was hit by a tornado. Most of the AEs were mild to moderate in severity. The most common AEs were seen in the neurological, psychiatric, and GI systems and included sedation, insomnia, headache, somnolence, abdominal pain, anxiety, decreased appetite, nausea, vomiting, fatigue, depressed mood and suicidality. Details of AEs from each study are provided in the investigator's brochure (IB). There were no meaningful safety differences between subjects exposed to ecopipam or placebo from physical examinations, laboratory tests, ECGs, C-SSRS and systematic assessments using scales to assess co-morbidities in children and adolescents. In addition to above evaluations for safety the impact of ecopipam on movement disorders has been studied using scales such as the AIMS, BARS and ESRS and no differences have been seen between ecopipam and placebo treated subjects.

Thus, based on the overall safety profile seen in over 2900 subjects including healthy participants, with both children/adolescents and adults being treated, safety data from subjects studied in the following conditions (cocaine addiction, Lesch Nyhan Disorder, Pathological

gambling, obesity, schizophrenia, and Tourette's) ecopipam is safe to continue being studied in children, adolescents, and adults with TD.

5.3.2. Assessment of Benefit

A review of the efficacy evaluations for ecopipam in three studies conducted in subjects with TD reveals improvement on the YGTSS-TTS and other measures of illness severity from Baseline to Endpoint.

In a Phase 2a, open-label, non-randomized study (PSY301), the activity and safety of ecopipam in 18 adult subjects with TD was evaluated. Subjects were to receive ecopipam HCl 50 mg for 2 weeks followed by 100 mg for 6 weeks. The primary outcome measure was the YGTSS-TTS. After ecopipam treatment, the YGTSS-TTS, motor tics score, phonic tics score and overall impairment decreased from Baseline to Endpoint, suggesting that the severity of tics was decreased.

In a Phase 2 randomized, double-blind, placebo-controlled, crossover study in children and adolescents (ages 7-17 years) with TD (PSY302), 40 subjects were enrolled and 38 (95.0%) completed the study. The primary endpoint was the YGTSS-TTS.

Ecopipam treatment resulted in a numerical decrease in the YGTSS-TTS relative to the placebo treatment, but the decrease was not statistically significant. The least squares mean (±SE) of the difference between ecopipam, and placebo treatm nt were -3.7; 95% CI, -0.9 to -6.5 P=0.011on Day 16 and -3.2; 95% CI, -0.3 to -6.1 P=0.0332 on Day 30.

In a Phase 2b randomized, double-blind, placebo-controlled, parallel-group study conducted in 153 children and adolescents (ages 6-18 years) with TD (EBS-101-CL-001), a statistically significant (p=0.011, LS mean [SE] difference: -3.4 [1.4], 95% CI: -6.1, -0.8) improvement in the YGTSS-TTS from BL to Week 12 was observed for ecopipam compared to placebo (30% average reduction from BL to Week 12 for ecopipam treated patients, treatment effect size = 0.48) and at all earlier timep ints beginning at Week 4. Mean change from BL to Week 12 was significant on the key secondary endpoint, CGI-TS-S (p=0.027). Significant improvement also occurred on many secondary endpoints. Ecopipam had activity on both motor and phonic tics as well as measures of overall function in patients with TD, as rated by the clinician and caregiver.

Based on the available safety data, there are several safety advantages for ecopipam compared to D2 antagonists, specifically with respect to lack of EPS-related adverse events, other adverse movement events, metabolic events, and lack of weight gain.

An individual subject may not receive any therapeutic benefit from participating in an investigational study however, by contributing to medical research, others will be helped. All subjects participating in the study will receive physical examinations, various laboratory tests, ECGs and a systematic evaluation of their condition. Ecopipam may help improve symptoms for participants.

5.3.3. Methods to Minimize Risks

The following steps are incorporated in the protocol to minimize risks to subjects:

- Subjects will be screened by an Eligibility Review study team for determination of their appropriateness to participate.
- All subjects will be evaluated for safety at least every four weeks while receiving study medication.
- All assessment instruments will be administered by raters trained by the rater training group for the relevant scale/instrument. To the extent possible, the same caregiver(s) should complete the questionnaires and interviews from the same rater at each applicable visit.
- All subjects will be evaluated using the following scales to assess possible worsening of other psychiatric symptoms or other side effects:
  - Columbia Suicide Severity Rating Scale (C SSRS) for all subjects
  - Children's Depression Rating Scale (CDRS-R) for children and adolescents
  - Patient Health Questionnaire-9 (PHQ-9) for adults
  - Pediatric Anxiety Scale (PARS) for children and adolescents
  - Hamilton Rating Scale for Anxiety (HAM-A) for adults
  - Extrapyramidal Symptom Ra ing Scale (ESRS) for all subjects
  - Children's Yale-Brown Obsessive-Compulsive Scale-II (CY-BOCS-II) for children and adolescents
  - Yale-Brown Obsessive-Compulsive Scale-II (Y-BOCS-II) for adults
  - Swanson, Nolan and Pelham Questionnaire (SNAP-IV-26) for children and adolescents
  - Conners Adult ADHD Rating Scale Self Report, Short Version (CAARS-S:S) for adults

In summary, ecopipam is a new chemical entity with a novel mechanism of action that has clinical evidence that it may be of therapeutic benefit to subjects with TD. There is also evidence that it is likely to have lower side effect burden (for EPS- and other movement-related adverse events, adverse metabolic events and lack of weight gain) than the currently used D2-receptor antagonists. The protocol has processes to minimize potential risks from study medication that participants may be exposed to such that risks from the study balance the potential benefits.

6. STUDY OBJECTIVES AND PURPOSE

6.1. 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 TD.

6.2. Secondary Objectives

The secondary objectives of this study are to evaluate the safety and tolerance of ecopipam dosed at 1.8 mg/kg/day (2 mg/kg/day ecopipam HCl) in children (≥ 6 and < 12years 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.

6.3. 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 11.3.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

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 to 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).

Eligibility Review is an evaluation and quality oversight process of subject eligibility. Sites will complete an Eligibility Review packet at Screening which includes key medical information (e.g., laboratory results, ECG, medical history, physical examination, concomitant medications), scales data (e.g., subject questionnaire responses), and any other information necessary to establish subject eligibility per protocol. A decision to enroll a subject will be made by the investigator only after the Eligibility Review is concluded. The investigator remains responsible for ensuring that subjects are eligible for enrollment.

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 (2 mg/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 a those with ≥ 25% improvement from Baseline (Day 1) on the YGTSS-TTS at both Weeks 8 & 12 during the open-label Stabilization period, will be randomized to ecopipam 1.8 mg/kg/day (ecopipam HCl 2 mg/kg/day) 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 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).

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 who discontinue the study prematurely for any reason will be tapered off ecopipam in decrements of 22.4 mg/day (25 mg/day ecopipam HCl) 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 followed by a telephone call 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-391within 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.

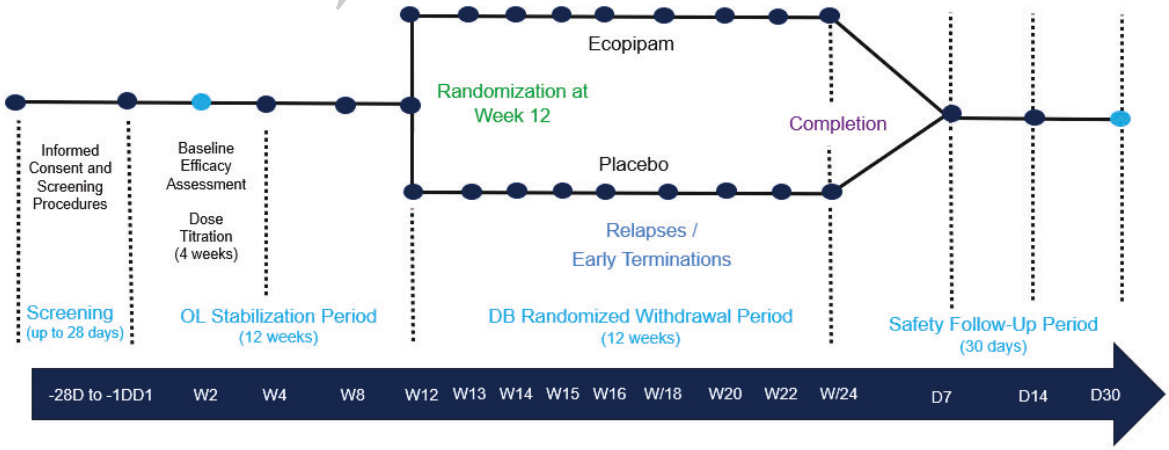
Responders to ecopipam who complete the R/WD period and who complete the Week 24/ Relapse/ET visit and the Day 7 and 14 follow-up visits are eligible to enter the long-term open-label study EBS-101-TD-391. Subjects who meet the criteria for Relapse and complete the Week 24/Relapse/ET visit and the Day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

In anticipation of reaching the target number of Relapse events, randomization into the double-blind R/WD period may be closed, at which time subjects in the open-label Stabilization period may continue in the study until the Week 12 visit. Upon completion of the Week 12 visit, subjects will have the opportunity to enter 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 has been completed.

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



7.2. Number of Subjects

The planned number of Relapse events for the double-blind R/WD period is 49 for children and adolescents (age ≥ 6 to < 18 years of age). 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). Assuming the proportion of subjects who Relapse in the double-blind R/WD period is 65% in the placebo group and 34% in the ecopipam group, approximately 98 children and adolescent subjects (49 subjects per group) will be required to achieve this number of events. Subject enrollment will stop around the time that 49 Relapse events for children and adolescents are expected to have occurred. The number of Relapses among adults will not determine study completion.

To randomize 98 children and adolescent subjects (≥6 to < 18 years of age), approximately 196 child and adolescent subjects will need to be enrolled assuming the Responder rate in the open-label Stabilization period is 50%.

Adult subjects with TD who meet all inclusion criteria and none of the exclusion criteria are eligible to enroll in the study. Since the symptoms of TD sh w improvement with age and a majority of adult patients exhibit minimal symptoms or are asymptomatic, it is anticipated that a minority of study participants will be adults. Hence it is anticipated that approximately 40 adults with TD will enter the open-label Stabilization period of this study.

7.3. Treatment Assignment

Responders to ecopipam in the open-label Stabilization period will be randomized 1:1 to either ecopipam or matching placebo for the R/WD period. Randomization assignment will be stratified by weight.

7.4. Dose Adjustment Criteria

Study drug is packaged for titration up t the target dose based on the subject's weight at Baseline according to the following weight bands to better achieve the targeted 1.8 mg/kg/day ecopipam (2 mg/kg/day ecopipam HCl) target dose: ≥18 to ≤23 kg, >23 to ≤34 kg, >34 to ≤44 kg, >44 to ≤68 kg, >68 to ≤83 kg, >83 kg. Those who cannot tolerate the target dose will be withdrawn from study. Dose assignment (based on weight) will not change during the duration of the study even if subject's weight changes. Study drug is packaged for taper down in decrements of 25 mg/day until off study drug. See Section 10.5 for direction on administration of study drug.

7.5. Criteria for Subject Study Discontinuation

A subject may elect to discontinue from the study at any time for safety or personal reasons. All subjects who discontinue from the study should complete the early termination procedures.

Any subject with a new positive response on questions 4 and/or 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) will be immediately discontinued and evaluated for risk.

Any subject with a CDRS-R or PHQ-9 assessment indicative of the onset of a new depressive episode at any visit can be discontinued from study participation at the discretion of the

Investigator. The Investigator will perform suicide risk assessment in subjects who respond positively to PHQ-9 question 9.

Subjects will be discontinued due to attempted suicide or suicidal behavior, oculogyric crisis, neuroleptic malignant syndrome, new onset seizures, serotonergic syndrome, or tardive dyskinesia. Subjects will also be discontinued if there are any adverse events that are Grade 4 (life-threatening consequences; urgent intervention indicated) in severity per CTCAE version 5.

Subjects who discontinue early from the study will be evaluated for one of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, loss of efficacy, and administrative/other. In addition to the primary reason, the subject may have indicated one or more of these reasons as secondary reasons for discontinuation. Study disposition information will be collected on the CRF.

Subjects who discontinue treatment for any reason, other than an SAE (even if the SAE is not treatment related) or an AE (unless the AE can be determined to be unrelated to treatment), may be replaced only after consultation with Sponsor or its designee

7.6. Criteria for Study Termination

The Sponsor may suspend or terminate the study, or part of the study, at any time for any reason including, but not limited to, safety and lack of efficacy

If the Sponsor, investigator, or regulatory agency officials discover conditions arising during the study that indicates that the study should be halt d or that a study site should be closed, this action may be taken after appropriate consul ation between the Sponsor, its designee, and the site investigator. If the study is suspended or terminated, the Sponsor or its designee will ensure that applicable sites, regulatory health authorities, and IRBs/ECs are notified as appropriate.

Table 3: 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)	W1 / VISIT 9 / Day 113 (± d)	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[b]	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	
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		

Visit/TC Study Day	Screening Period[a] Screening VISIT 1 Day -28 to -1	Open-Label Stabilization Period Titration Phase Baseline VISIT 2 Day 1	 W 2 [f] Day 15 Telephone call only (±3d)	Maintenance Phase Weeks 4 to 12 (Day 29 up to 84) W4 / VISIT 3/ Day 29 (±3d)	 W8 / VISIT 4 / Day 57 (±3d)	 W 12 VISIT 5 Day 85 (±3d)	Double-Blind Randomized Withdrawal Period Weeks 12 to 24 (Days 85 to 169) 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)	Safety Follow-Up (Days 170-199) 7 Day F/U VISIT 14 (±3d)	 14 Day F/U VISIT 15 (±3d)	 30 Day F/U[f] Telephone call only (±3d)
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			
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			

	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)
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			
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	

	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)
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 pr cedures 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) height and weight.
Neurological exam should be part of the physical exam. Physical exam t Week 4 visit will include assessment for serotonin syndrome. If serotonin syndrome symptoms are present, local laboratory assessment should be performed.

[c] Subjects should be in a fasting state (8 hours) for laboratory t sts. Fas ing 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.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Inclusion Criteria

1) If <18 years of age, subject's parent or legal guardian must sign a written informed consent and subject must sign a written informed assent according to the requirements of the site's IRB/EC. If ≥18 years of age, subject must sign a written informed consent according to the requirements of the site's IRB/EC.
2) Subjects must be ≥6 years of age at time of screening.
3) Subjects must weigh at least ≥18 kg (39.6 lbs.).
4) Subjects must have TD based on Diagnostic and Statistical Manual for Mental Disorders – 5th Edition (DSM-5-TR diagnostic criteria) for TD.
5) Subjects must exhibit both motor and vocal tics that cause impairment with normal routines.
6) Subjects must have a minimum score of 20 on the YGTSS-TTS at Screening and at Baseline visits with tic symptoms causing impairment in the subject's normal routines, including academic achievement and/or occupational functioning, and/or social activities, and/or relationships or whose symptoms distress the subject to the extent that treatment is appropriate
7) Female participants of childbearing potential must agree to use a highly effective method of contraception (i.e , pregnancy rate of less than 1% per year) during the study and for 30 days after the discontinuation of the IMP. Adequate contraceptive methods include combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception with inhibition of ovulation (oral, injectable, implantable), intrauterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal occlusion, vasectomized male partner, or a female participant who is not of childbearing potential.

   Female participants and female partners of male study participants using a hormonal contraceptive must also use a barrier method (i.e., condom or occlusive cap [diaphragm or cervical/vault caps]) and should have been stable on their hormonal contraceptive treatment for at least 4 weeks prior to Screening.
8) Sexually active male subjects must use a highly effective method of contraception during the study and agree to continue the use of highly effective contraception for at least 30 days after the last dose of study drug.
9) For sites in the EU only, the subject must have received an adequate trial of non-pharmacological therapy without adequate response prior to study enrollment.

8.2. Exclusion Criteria

Individuals meeting any of the following criteria at Screening or Baseline are ineligible to participate in the study:

1) Subjects with previous exposure to ecopipam (e.g., participated in study PSY301, PSY302 or EBS-101-CL-001).
2) Subjects with any unstable mood disorder (DSM-5-TR criteria) at Screening or Baseline.
3) Subjects who have unstable medical illness or clinically significant abnormalities on laboratory tests, or ECG at Screening as determined by the Principal Investigator.
4) Subjects with a significant risk of attempting suicide based on history (suicide attempt in past 1 year or who have had 2 or more lifetime suicide attempts) or who had an answer of ‘‘yes’’ on any question other than 1–3 (currently or within the past 30 days) on the baseline/screening version of the Columbia Suicide Severity Rating Scale (C-SSRS).
5) Subjects with a clinical presentation at Screening or Baseline and/or history consistent with another neurologic condition that may have had accompanying abnormal movements (e.g., Huntington’s disease, Parkinson’s disease, Wilson’s disease, stroke, Restless Legs Syndrome).
6) Female subjects who are currently pregnant or lactating or planning to become pregnant during the study.
7) Subjects who have moderate to severe renal impairment.
8) Subjects who have hepatic impairment at Screening.
9) Subjects with current or recent (past 3 months) history of DSM-5-TR substance use disorder (except for nicotine).
10) Subjects with positive urine drug screen for cocaine, amphetamine, benzodiazepines, barbiturates, phencyclidine (PCP), or opiates at Screening, except those receiving stable, prescribed treatme t for attention deficit/hyperactivity disorder (ADHD).
11) Subjects with a ≥25% difference in the absolute change in YGTSS-TTS between the Screening visit and the Baseline visit.
12) Subjects with a lifetime history of bipolar disorder type I or II, dementia, schizophrenia, or any other psychotic disorder.
13) Subjects with an onset of a major depressive episode in the past 6 months.
14) Subjects with a PHQ-9 score of ≥10 at Screening or Baseline.
15) Subjects with a history of seizures (excluding febrile seizures that occurred >2 years prior to Screening).
16) Subjects with a history of neuroleptic malignant syndrome.
17) Subjects with a myocardial infarction within 6 months prior to Screening.
18) Subjects who have had previous treatment with:
    - investigational medication within 4 weeks prior to Screening
    - oral neuroleptics within 4 weeks prior to Screening
    - depot neuroleptics within 3 months prior to Screening (e.g., risperidone microspheres) or 6 months prior to screening (e.g., paliperidone palmitate)
19) Subjects receiving any other medication to treat motor or vocal tics for at least 14 days prior to Baseline.

20) Subjects receiving unstable doses or excluded medications to treat depression, anxiety or ADHD for a minimum of 4 weeks prior to Screening.
21) Subjects who have a need for medications which would have unfavorable interactions with ecopipam, e.g., CYP2D6, CYP3A4, CYP2C19, P-gp, substrates with a narrow therapeutic window (e.g., digoxin), inhibitors of CYP2D6 (e.g., fluoxetine), broad-spectrum UGT enzyme inhibitors (e.g., valproic acid), dopamine antagonists (e.g., neuroleptics) or agonists (including bupropion), tetrabenazine, VMAT-2 inhibiters (e.g. tetrabenazine), tricyclics and tetracyclics, monoamine oxidase inhibitors, or St. John's Wort. See Section 23.
22) Subjects who have initiated new psychological therapies or deep brain stimulation within 10 weeks prior to Baseline visit.
23) Initiation or changes in psychological therapies during the study (i.e., Habit Reversal Training or Comprehensive Behavioral Intervention for Tics) as well as deep brain stimulation.
24) Subjects unable to swallow tablets.
25) Subjects with a known hypersensitivity to any excipients of ecopipam tablets, including subjects with confirmed lactose intolerance.
26) Subjects who are employed by the sponsor, vendors working on the study, study site personnel or their family members.
27) Siblings or family members of any current subject participating in the study.
28) Subjects deprived of liberty by administrative or judicial decision, patients under court protection, guardianship curatorship or family guardianship.
29) Any subject who in the opinion of the investigator is not a suitable candidate for the study.

8.3. Subject Withdrawal, Removal, and Replacement Criteria

Any subject with a new positive response on questions 4 and/or 5 of the C-SSRS will be immediately discontinued and evaluated for risk.

Any subject with a CDRS-R or a PHQ-9 assessment indicative of the onset of a new depressive episode at any visit can be discontinued from study participation at the discretion of the Investigator.

Subjects will be discontinued due to attempted suicide or suicidal behavior, oculogyric crisis, neuroleptic malignant syndrome, new onset seizures, serotonergic syndrome, or tardive dyskinesia. Subjects will also be discontinued if there are any adverse events that are Grade 4 (life-threatening consequences; urgent intervention indicated) in severity per CTCAE version 5. The Investigator or subject may choose to stop study treatment at any time for safety or personal reasons. Where possible, a subject who discontinues treatment will undergo protocol-specified end-of study procedures at the time of discontinuation. Date and reason(s) of premature discontinuation will be described in the CRF.

Subjects who discontinue treatment for any reason, other than an SAE (even if the SAE is not treatment related) or an AE (unless the AE can be determined to be unrelated to treatment), may be replaced only after consultation with Sponsor or its representative.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

Table 4: Investigational Product

	Investigational product	
Product Name	Ecopipam	Placebo
Dosage Form	Tablets	Matching tablets
Unit Dose of Ecopipam	11.2, 22.4, 33.6, 44.8, 67.2 and 89.6 mg	Matching unit dose tablets
Unit Dose of Ecopipam HCl	12.5, 25, 37.5, 50, 75 and 100 mg	
Route of Administration	Oral	Oral
Physical Description	Round, biconvex, light blue film-coated tablet, plain on both side	Round, biconvex, light blue film-coated tablet, plain on both side
Manufacturer	Catalent Pharma Solutions, LLC	Catalent Pharma Solutions, LLC

9.2. Concomitant Medications

For subjects who receive study treatment, any medication (including over-the-counter medications) administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication CRF. Nonpharmacologic therapies/procedures will also be captured on the CRF. The Investigator will record any AE on the Adverse Events CRF for which the concomitant medication was administered.

9.2.1. Allowable Medications for Common Comorbid Conditions

The following medications are allowed for the treatment of subjects with ADHD, anxiety, depression, mood disorder, and OCD if doses have been stable for at least 4 weeks prior to Screening and the dose is not expected to change and remains stable during the course of the study.

Allowable stimulants for comorbid ADHD

- Amphetamine
- Dextroamphetamine
- Amphetamine and dextroamphetamine (mixed salts)

- Dexamphetamine
- Dexmethylphenidate
- Lisdexamfetamine
- Methylphenidate

Allowable medications for anxiety, mood disorders, depression and OCD

- citalopram
- desvenlafaxine
- escitalopram
- fluvoxamine
- levomilnacipran
- milnacipran
- sertraline

Anxiolytics

- lorazepam - Chronic use only
- hydroxyzine

9.3. Prohibited Therapies

Since ecopipam and its metabolite (EBS-101-40853) may inhibit CYP2D6, OATP1B1, P-gp and UGT1A9 and induce CYP3A4 and CYP2C19, for any drug that is a substrate of these enzymes, the label for the drug should be co sulted to decide if a dose adjustment is needed.

Prohibited therapies per the exclusion criteria (Section 8.2) include:

- Previous treatment with ecopipam
- Any investigational medication within 1 month prior to Screening
- Oral neuroleptics within 4 weeks prior to Screening
- Depot neuroleptics within 3 months prior to Screening (e.g., risperidone microspheres) or 6 months prior to screening (e.g., paliperidone palmitate)
- Any medications for the treatment of tics for at least 14 days prior to Baseline
- Subjects receiving unstable doses or excluded medications to treat depression, anxiety or ADHD for a minimum of 4 weeks prior to Screening.
- Subjects who have a need for medications which would have unfavorable interactions with ecopipam, e.g., CYP2D6, CYP3A4, CYP2C19, P-gp, substrates with a narrow therapeutic window (e.g., digoxin), inhibitors of CYP2D6 (e.g., fluoxetine), broad-spectrum UGT enzyme inhibitors (e.g., valproic acid), dopamine antagonists (e.g.,

neuroleptics) or agonists (including bupropion), tetrabenazine, VMAT-2 inhibiters (e.g. tetrabenazine), tricyclics and tetracyclics, monoamine oxidase inhibitors, or St. John's Wort. See Section 23.

- New psychological therapies that were initiated within 10 weeks prior to the Baseline visit
- Initiation or changes in psychological therapies during the study (i.e., Habit Reversal Training or Comprehensive Behavioral Intervention for Tics) as well as deep brain stimulation.

An illustrative, but not complete, list of excluded drugs is provided in the Prohibited Medications List in Section 23.

9.4. Treatment Compliance

During the study period, subject compliance will be monitored by review of the unused tablet counts at the study site visits. Less than 80% compliance will require evaluation by the Investigator and Sponsor or its representative to determine if the subject may continue the study.

9.5. Randomization and Blinding

Randomization will be stratified by weight band. Throughout the study, subjects, caregivers, and all personnel involved with the conduct and interpretation of the study, including the 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 CRO 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 the IWRS user manual. The site will be trained in this process and should only be used in an emergency. These codes should only be broken if knowledge of the subject's randomization code will affect his/her medical treatment. If necessary, the Investigator may consult with the sponsor before breaking the blind. The Investigator is to record the date and time of requesting the code and the reason for breaking the code.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Ecopipam tablets and matching placebo tablets.

10.2. Study Drug Packaging and Labeling

Study drug will be supplied in labeled containers by the Sponsor. The product release certificates for ecopipam tablets will be included in the clinical study report for this protocol. Any special storage conditions will be noted on the label and should be followed by the study site.

The labels will be produced by PCI Pharma Services. Minimally, the labels will contain the following information. This will be adapted for any local laws and regulations:

1. Name, address, and telephone number of the Sponsor
2. Pharmaceutical dosage form, route of administration, quantity of dosage units, identifier, and dose strength
3. Lot number
4. Protocol Number
5. Study subject identification number
6. Directions of use
7. "Caution: New Drug – Limited by Federal (US) law to investigational use" (or equivalent for rest of world)
8. Storage Conditions
9. Expiration Date

10.3. Study Drug Storage

Study drug is to be stored at 59ºF to 77ºF (15ºC to 25ºC) protected from light, excessive heat, open flame and combustibles, out of direct sunlight, and in a well-ventilated, dry area.

All relevant site-specific guidelines and country-specific labeling requirements must be followed. Study drug must be kept in a secure location and carefully stored at the study site within its original container. A daily temperature log for monitoring of proper storage conditions must be maintained by the site.

10.4. Study Drug Preparation

Study drug primary packaging will be in blister packs for ecopipam and matching placebo. No preparation is required.

10.5. Administration

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 5):

Table 5: 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 f r each of he 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 the 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 meets Relapse criteria during the R/WD period, or who discontinues 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.

10.6. Dosing Rationale

A dosage regimen of 1.8 mg/kg/day ecopipam (2 mg/kg/d ecopipam HCl) was chosen based on the results of a randomized, double-blind, placebo-controlled, parallel group study (Study EBS-101-CL-001) of 153 subjects with TD aged 6-18 years receiving ecopipam at a dose of 1.8 mg/kg/day (ecopipam HCl 2 mg/kg/day) after a 3- to 4-week titration which demonstrated that ecopipam was significantly superior to placebo in reducing tic severity as shown by reduction in the YGTSS-TTS) and that the safety profile was acceptable.

10.7. Study Drug Accountability

The Investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site use for each subject, and return of the study drug to a delegate of the Sponsor. Total study site accountability will be conducted at the end of the study and the Investigator must explain all discrepancies.

A Drug Dispensing Log must be kept current and should contain the following information:

- Identification (subject number and initials or as allowed per local requirements) of subject to whom the study drug was dispensed
- The dates and lot numbers for the study drug dispensed
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the Clinical Research Associate (CRA).

Due to the COVID-19 pandemic, in some cases direct to patient shipments may be made if acceptable according to country regulations. In Germany, these procedures are not possible after December 31, 2023. In these cases, study medication may be transported to the subject by a third-party vendor who has systems in place to protect blinding, patient privacy, and data integrity.

On close-out of the site, all used and unused investigational product must be shipped to the Emalex-designated location. The Drug Dispensing Log must be available for monitoring, auditing, or inspection.

10.8. Study Drug Handling and Disposal

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (e.g., pharmacist), and that:

- Such deliveries are recorded;
- Study drug is handled and stored safely and properly;
- Study drug is only dispensed to study subjects in accordance with the protocol;
- Any unused study drug is returned to the sponsor or standard procedures for the alternative disposition of unused study drug are followed.

11. ASSESSMENT OF EFFICACY

All assessment instruments will be administered by raters trained by the rater training group for the relevant scale/instrument. The same rater should conduct the assessment for the same subject and as much as possible, the same caregiver(s) should complete the questionnaires and interviews.

Age-appropriate scales/instruments are determined by the subject's age at the time of Informed Consent and will not be adjusted if the subject's age changes during their participation in the study.

Assessments may be completed in locations other than study clinic and/or via remote administration due to restrictions because of the COVID-19 pandemic or other qualifying event if acceptable according to country regulations. In Germany, these procedures are not possible after December 31, 2023.

11.1. Primary Efficacy Assessment

The primary efficacy endpoint for this trial is the time from Randomization (Week 12) to Relapse, defined as the loss of ≥50% of the improvement experienced in 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 in subjects between the ages of ≥ 6 and <18 years for ecopipam compared to those receiving placebo during the double-blind, R/WD period.

11.1.1. Yale Global Tic Severity Scale (YGTSS)

The YGTSS is a clinician-rated, multi dimensional instrument for assessing tic symptom severity in children and adults with TD.[19] It includes a semi-structured interview with either a caregiver (for subjects <18 years of age) or adult subjects (≥18 years of age) and clinical observations that assess tic and tic-related impairment s verity 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).

The lookback period is over the previous week. Administration time is approximately 15 minutes.

11.2. Secondary Efficacy Assessment

The secondary efficacy endpoint in this trial is the 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.

11.3. Exploratory Efficacy Assessments

- 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 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 another secondary endpoint with agreement from Health Authorities.
- 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 another secondary endpoint with agreement from Health Authorities.
- Mean change from Randomization (Week 12) to Week 24 in the YGTSS-TTS for ecopipam compared to placebo.
- Mean change from Randomization (Week 12) to Week 24 in the Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) for ecopipam compared to placebo.
- Mean change from Randomization (Week 12) to Week 24 in the YGTSS-Global Severity (GS) score for ecopipam compared to placebo.
- Mean change from Randomization (W ek 12) to Week 24 in the Caregiver Global Impression of Change (CaGI-C) for ecopipam compared to placebo.
- Time from Randomization (Week 12) to a loss of ≥ 50% of the improvement from Baseline (Day 1) experienced on the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) at the last visit (Week 12) in the open-label Stabilization period.
- 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.
- Mean change from Randomization (Week 12) to Week 24 in the Premonitory Urge for Tics Scale (PUTS) for ecopipam compared to placebo.
- 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.
- 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.
- Mean change from Baseline (Day 1) to Week 12 in the YGTSS-TTS.
- 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.
- Mean change from Baseline (Day 1) to Week 24 in the YGTSS-TTS for ecopipam compared to placebo.
- Mean change from Baseline (Day 1) to Week 24 in the YGTSS-GS score for ecopipam compared to placebo.
- 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.

- Caregiver Global Impression of Change (CaGI-C) through Week 24 for ecopipam compared to placebo.
- Mean change from Randomization (Week 12) to Week 24 in Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) for ecopipam compared to placebo.
- Mean change from Baseline (Day 1) to Week 24 in the Clinical Global Impression of Tourette Syndrome Improvement (CGI-TS-I) for ecopipam compared to placebo.
- Time from Randomization (Week 12) to treatment discontinuation during the double-blind R/WD period for ecopipam compared to placebo.
- Time from Randomization (Week 12) to loss of ≥ 100% of the improvement experienced on the Yale Global Tic Severity Scale- Total Tic Score (YGTSS-TTS) from Baseline (Day 1) to the last visit (Week 12) in the open-label Stabilization period for ecopipam compared to placebo.
- To evaluate the population PK/pharmacodynamic (PD) relationships with ecopipam during the open-label Stabilization period of the study.

Additional analyses will include efficacy endpoints listed above at all earlier timepoints and the YGTSS subscales individually (Motor, Vocal, and Impairment). The correlation between subjects meeting Relapse criteria based on YGTSS-TTS and those who also had at least a 1-point reduction on CGI-TS-S will also be investigated. If there is a strong correlation between subjects ≥6 and <18 years who meet Relapse criteria based on the YGTSS-TTS and have a worsening by at least one category of the CGI-TS-S, Relapse will not be a competing risk, and therefore the time to worsening of the CGI-TS-S for subjects ≥6 and <18 years will be considered a secondary endpoint. Similarly, if there is a strong correlation between all subjects irrespective of age who meet Relapse criteria based on the YGTSS-TTS and have a worsening by at least one category of the CGI-TS-S, Relapse will not be a competing risk, and therefore the time to worsening of the CGI-TS-S for all subjects irrespective of age will be considered a secondary endpoint.

Subgroup analyses will also be conducted on all efficacy endpoints listed above for the following populations:

- Children (≥ 6 and < 12 years of age), Adolescents (≥ 12 and < 18 years of age), and Adults (≥ 18 years of age)
- Subjects per region
- 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)

Rank order of hierarchy of the secondary and exploratory endpoints will be outlined in the statistical analysis plan.

11.3.1. Clinical Global Impression Tourette Syndrome (CGI-TS)[20,12]

The CGI-TS provides an overall clinician-determined summary assessment that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

Administered by an experienced clinician familiar with the disease under study and the likely progression of treatment, the CGI rater can make an expert clinical global judgment about the severity of the illness across various time points within the context of that clinical experience. The clinician makes a judgment about the total health of the subject at each visit: the illness severity, the subject's level of distress and other aspects of impairment, and the impact of the illness on functioning. The CGI is rated without regard to the clinician's belief that any clinical changes are or are not due to medication and without consideration of the etiology of the symptoms.

The CGI consists of two reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms. The severity scale (CGI-S) ranges from 1 (Normal, not ill) to 7 (extremely ill). The improvement scale (CGI-I) ranges from 1 (very much improved) to 7 (very much worse) with a score of 1 or 2 defining positive resp nse. Pediatric and adult versions of the CGI-TS-S and CGI-TS-I scales are available and will be administered according to the age of the subject at the time of Informed Consent.

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 as ist, accommodate, or support the subject should be considered in overall severity in the case of pediatric subjects.

The improvement rating compares the subject's overall clinical condition to the Baseline visit and the rater should consider the following question: "Compared to tic severity at baseline, how much has the subject changed?" The two CGI-TS scores can occasionally be dissociated such that a clinician may notice changes in the CGI-I relative to baseline despite no recent changes in the overall CGI-S score or vice versa.[21]

The look back period is past 7 days. Administration time is approximately 5 minutes.

11.3.2. Caregiver Global Impression of Change (CaGI-C)[12]

The CaGI-C is a short scale completed by the caregiver(s) of subjects <18 years old. It consists of an 8-item Likert scale ranging from 0 (Not rated) to 7 (Very much worse).

The caregiver will rate whether the subject's overall TD symptoms change since the beginning of the study (prior to starting study drug). Completion time is approximately 5 minutes.

11.3.3. Premonitory Urge for Tics Scale (PUTS)[22]

The PUTS is designed as a self-reported scale to measure tic-related premonitory urges. In this study, the rater will read the questions to 6-17 year-old subjects and record their responses. The PUTS consists of a 9-item Likert scale with each item ranging from 1 (Not at all true) to 4 (very much true). Total scores range from 9 to 36 with higher scores indicative of worse severity.

The lookback period is over the past week. Administration time is under 5 minutes.

11.3.4. Gilles de la Tourette Syndrome – Quality of Life scale for Children aged 6-12 years and Adolescents aged 13-18 years (C&A GTS-QOL)[16]

The C&A GTS-QOL is a 27-item questionnaire completed through a clinician-rated interview for subjects aged 6-12 years and a self-report questionnaire for subjects aged 13-18 years. In this study, 18-year-olds are defined as adults and will complete the adult version (GTS-QOL). The instrument assesses 4 areas of health-related quality of life: psychological, physical/activities of daily living, obsessive–compulsive, and cognitive domains. Each item is rated on a 5-point Likert-type scale. 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.

The lookback period is 4 weeks. Administration time is approximately 15 minutes.

11.3.5. Gilles de la Tourette Syndrome – Quality of Life Scale (GTS-QOL)[23]

The GTS-QOL is a 27-item questionnaire completed by adult subjects aged >18 years. In this study, 18-year-olds are defined as adults and will complete this adult version. The instrument assesses 4 areas of health-related quality of life: psychological, physical/activities of daily living, obsessive–compulsive, and cognitive domains. Each item is rated on a 5-point Likert-type scale. 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.

The lookback period is 4 weeks. Completion time is approximately 10 minutes.

11.4. Pharmacokinetics Assessments

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

Subjects and parents/caregivers (as applicable) will be instructed to skip their at-home administration of study medication on the evening prior to the Week 4 visit and to record the date and time the 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 three time windows: predose (34 to 44 hours since the last dose), between 0.5 and 1.5 hours after administration of study medication, and between 2 and 4 hours after study drug administration. Any samples should be collected at least 30 min apart.

At Weeks 8 or 12 visit, subjects and parents/caregivers (as applicable) will be asked to record the date and time of the last dose of study medication taken. The time of blood sample collection will be recorded. Blood samples will be processed as outlined in the laboratory manual and analyzed for ecopipam and its major metabolite EBS-101-40853.

12. ASSESSMENTS OF SAFETY

All assessment instruments will be administered by raters trained by the rater training group for the relevant scale/instrument. The same rater should conduct the assessment for the same subject and as much as possible, the same caregiver(s) should complete the questionnaires and interviews.

Age-appropriate scales/instruments are determined by the subject's age at the Baseline visit and will not be adjusted if the subject's age changes during their participation in the study.

Assessments may be completed in locations other than study clinic and/or via remote administration due to restrictions because of the COVID-19 pandemic or other qualifying event if acceptable according to country regulations. In Germany, these procedures are not possible after December 31, 2023.

12.1. Safety Parameters

Safety will be assessed by monitoring and recording all adverse events (AEs) and Serious Adverse Events (SAEs) at all Visits, regular monitoring of hematology, blood chemistry, urinalysis, and prolactin (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. All subjects will be monitored for signs or symptoms signs or symptoms of withdrawal, abuse and dependence.

12.1.1. Columbia Suicide Severity Rating Scale (C-SSRS)[10]

The C-SSRS[10] is a low burden instrument to assess both suicidal behavior and ideation. Questions are phrased for use in an interview format. 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. The scale is appropriate for subjects from age 6 through to an elderly population.

The clinician interview time is approximately 10 minutes.

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

The CDRS-R[15] is a semi-structured clinician interview-based instrument. Originally designed for 6-12 years old, it is the most commonly used scale in adolescent depression research.[24] In this study, children and adolescents aged 6-17 will be interviewed by the clinician. Seventeen symptom areas are assessed during the interview. Each item is rated on a scale of 1 to a maximum of either 5 or 7, with 1 being least severe (no difficulties) and 5 or 7 being 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.

The symptoms being evaluated by this scale are rated by the clinician as present or absent at the time of evaluation. Administration time is approximately 15 minutes.

12.1.3. Patient Health Questionnaire-9 (PHQ-9)[25]

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.

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 lookback period is 2 weeks. Completion time is less than 5 minutes.

12.1.4. Pediatric Anxiety Rating Scale (PARS)[17]

The PARS is a clinician-rated instrument for assessing the se erity of anxiety symptoms associated with common anxiety disorders and generalized anxiety in children and adolescents 6-17 years of age. The PARS is comprised of 2 sections: a 50-item symptom checklist grouped into 6 categories and 7 severity items. For the sympt ms checklist, the clinician interviews the caregiver(s) and child (separately or together) and rates each item as present (1=yes) or absent (2=no) during the previous week. The clinician will integrate the child and caregiver's endorsed symptoms to make severity ratings on 7 dimensions using a 6-point scale 0-5. Higher ratings indicate greater severity.

The lookback period is the past week. Administration time is approximately 30 minutes.

12.1.5. Hamilton Rating Scal for Anxiety (HAM-A)[26]

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

The lookback period is 1 week. Administration time is approximately 15 minutes.

12.1.6. Extrapyramidal Symptom Rating Scale (ESRS)[27]

The ESRS is a clinician-reported instrument developed to assess four types of drug-induced movement disorders (DIMD): Parkinsonism, akathisia, dystonia, and tardive dyskinesia. The ESRS consists of 2 parts:

Part A: 4 subscales:	Part B: 4 CGI-S scales assessing:
• A questionnaire of EPS or DIMD • An examination of Parkinsonism and akathisia	• Tardive dyskinesia • Parkinsonism

• An examination of dystonia • An examination of dyskinesia	• Dystonia • Akathisia

The lookback period is 7 days. Administration time is approximately 15 minutes.

12.1.7. Children's Yale-Brown Obsessive-Compulsive Scale-II (CY-BOCS-II)[28,29]

The CY-BOCS-II is a reliable and valid scale[14] 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.

The lookback period for each item is dichotomously rated. Administration time is approximately 10 minutes.

12.1.8. Yale-Brown Obsessive-Compulsive Scale-II (Y-BOCS-II)[30]

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.

The lookback period for each item is dichotomously rated. Administration time is approximately 10 minutes.

12.1.9. Swanson, Nolan and Pelham SNAP-IV-26)[13]

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.

It is rated by the caregiver(s) as present or absent at the time of evaluation on a 0-3-point scale. Completion time is approximately 10 minutes.

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

The CAARS[31] is a 26-item self-report questionnaire assessing ADHD symptoms in adults (ages 18 and older). Subjects are asked to rate themselves on a range of symptoms and behaviors associated with ADHD in adults, using a 4-point scale and the total score ranges from 0-78 with higher scores indicating greater severity.

It is rated by the subject as present or absent at the time of evaluation on a 0-3-point scale. Completion time is approximately 5 minutes.

12.1.11. Vital Signs

Vital signs [blood pressure (after being supine for 5 minutes), pulse, height (children and adolescents only) and weight] will be collected at each clinic visit per Table 3.

12.1.12. Electrocardiogram (ECG)

Sites will be provided with a 12-lead ECG device to complete assessments per Table 3. Clinicians will instruct subjects to follow-up with care as appropriate upon evidence of new or worsening abnormal ECG readings.

12.1.13. Central Laboratory Tests:

Subjects should be in fasting state (minimum of 8 hours) for all blood laboratory tests collected at study visits after the Screening visit, per Table 3.

Category	Test names
Hematology	Red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Hct), platelets, and white blood cell (WBC) count with differential (neutrophils, bands lymphocytes, monocytes, eosinophils, basophils, immature granulocyte) Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Mean Platelet Volume (MPV), Red Cell Distribution Width (RDW), CBC, Nucleated Red Blood Cell
Chemistry	Glucose, calcium, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, globulin, prolactin; Liver function tests: albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), total bilirubin, direct bilirubin, Calcium (Ca), Total cholest rol, glucose, lactate dehydrogenase (LDH), phosphorous, total protein, triglycerides; Electrolytes: sodium (Na), potassium (K), chloride (Cl), bicarbonate; Renal function tests: Blood urea/blood urea nitrogen (BUN), creatinine
Urinalysis	Complete urinalysis includes color, appearance, specific gravity, pH, protein, glucose, ketones, and blood with microscopic examination for positive protein or blood results
Pregnancy Test	A local urine test (for women of childbearing potential only) and central laboratory serum test to confirm a positive urine result
Urine Drug Screen	Central laboratory test to detect the presence of cocaine, amphetamine, benzodiazepines, barbiturates, phencyclidine (PCP), opiates
Special Test	Hemoglobin A1c (HbA1c) at Baseline, Week 12 and Week 24

Maximum blood volume to be drawn at each visit is noted below.

Visit	Maximum Blood Volume (mL)
Visit 1 – Screening	6
Visit 2 – Baseline	8
Visit 3 – Week 4	14
Visit 4 – Week 8	6
Visit 5 – Week 12	12
Visit 10 – Week 18	6
Visit 13 – Week 24/Relapse/ET	8
Visit 14 – 7 Day Follow Up	6
Visit 15 – 14 Day Follow Up	6

Total volume at each visit does not exceed 1% of the total blood volume and the total volume of all blood samples does not exceed 3% of the total blood volume.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diseas temporally associated with the use of a study drug, whether related to the study drug or not.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

12.2.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition including worsening of TD following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical

studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs that occur after any subject has been screened, enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether they are related to the study or not, must be recorded on forms provided by Sponsor or its representatives.

12.2.1.2. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator, or placebo, that fulfills one or more of the following:

- 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.

All SAEs that occur after any subject/subject h s been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether they are related to the study, must be recorded on forms provided by the Sponsor or its representatives.

12.2.1.3. Other Adverse Event (OAE)

OAEs will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the eval ation of safety data for the Clinical Study Report. Significant adverse events of clinical importance, other than SAEs and those AEs leading to discontinuation of the subject/subject from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in the Clinical Study Report. Adverse events of special interest (AESI) to characterize ecopipam are programmatically listed for review and will be identified by the Medical Director(s) and Drug Safety Physician. The AEs include weight gain, extra-pyramidal reactions and suicidal ideations and behavior.

12.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated”. If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered related to the Investigational Product for the purposes of expedited regulatory reporting.

12.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse can be reported as AEs per the investigator's judgement. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from the signing of consent form until the end of the study. SAE information will be collected from signing of consent form until 30 days following the last dose of study drug. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether it caused the subject to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.1.2. An AE of severe intensity may not be considered serious.

Should a pregnancy of a subject or partner occur, it must be reported and recorded on Sponsor's or Sponsor approved pregnancy form. Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Reports of pregnancy must be submitted without undue delay and no longer than 24 hours of awareness of the event:

Email Address: safetyreporting@syneoshealth.com
Fax no. Americas: +1 877 464 7787
Fax no. Europe and ROW +44 1628 461184

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.5. Reporting Serious Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of consent form until 30 days following the end of treatment exposure. Any SAE considered possibly or probably related to

the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported without undue delay and no longer than 24 hours of awareness of the event :

Email Address: safetyreporting@syneoshealth.com
Fax no. USA: +1 877 464 7787
Fax no. outside USA +44 1628 461184

The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy to the Sponsor or its representatives.

Additional follow-up information, if required or available, should all be sent to the Sponsor or its representatives without undue delay and no longer than 24 hours of awareness of the event and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

The Sponsor and its representatives are responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

13. STATISTICS

All data analyses will be performed by the Sponsor or its representatives after the study is completed, and the database is finalized and released. The statistical analyses described in this section will be performed using SAS 9.4. All collected data will be listed. Additional analyses may need to be conducted for data not collected at sites and/or via remote administration due to restrictions because of the COVID-19 pandemic or other qualifying event, details of these additional analyses will be specified in the SAP.

13.1. Analysis Population

The Modified Intention-to-Treat (mITT) population will include all randomized subjects who received at least one dose of study drug post randomization. The mITT population will be used for the analysis of primary, secondary and exploratory efficacy endpoints. All analyses performed for the mITT population will also be performed for the Intent-to-Treat (ITT) population defined as all randomized subjects.

The Per-Protocol (PP) population will include subjects from the mITT population 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 if subjects and/or data should be excluded from the PP Population. The list of subjects or observations to be excluded from the PP Population, 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.

The Safety population will include all subjects who received at least one dose of study drug. The safety population will be used for the analysis of the safety endpoints.

The Pharmacokinetics (PK) population will include all subjects from safety population who have a valid concentration measurement

13.2. Data Safety Monitoring Board

An independent data safety and monitoring board (DSMB) consisting 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.

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.

13.3. Interim Analysis

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). The 2-sided alpha level for the IA is 0.005. If statistical significance is reached at the IA, the DSMB can recommend stopping the study for overwhelming efficacy. If the study proceeds to the planned completion, the final 2-sided alpha level will be 0.0492. In addition to the possibility of stopping early for efficacy, a conditional power analysis will be performed to assess whether the total number of relapse events should be increased beyond 49 in order to increase statistical power at the final analysis. If the probability based on conditional power of a successful study is too small and does meet pre-specified criteria, the DSMB can recommend stopping the study for futility. If the probability of a successful study is reasonable, the DSMB can recommend continuing the trial as planned or can also recommend continuation of the trial with a sample size adjustment based on conditional power. Interpretation of conditional power will be guided by the promising zone approach.[32] One consequence of this approach is that no adjustment of the final alpha level will be required (other than the alpha spending of the IA). Full details will be provided in the Statistical Analysis Plan (SAP).

13.4. Planned Analysis

13.4.1. Efficacy Analysis

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 w rsening 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 obs rvations. 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 and PP populations according to the randomized treatment. Details will be provided in the Statistical Analysis Plan.

The time-to-event secondary and exploratory endpoints related to Relapse will be analyzed in a similar manner as the primary endpoint. The exploratory endpoints of mean change will be assessed with a Mixed Model for Repeated Measures (MMRM) model using the SAS MIXED procedure, with a REPEATED statement, with no imputation. The model will include fixed effects for treatment, visit, the interaction between treatment and visit, and a covariate for baseline score for the given assessment and other covariates such as gender, age group, race/ethnicity, and region. All secondary and exploratory endpoints will be analyzed in the mITT population according to randomized treatment. Details will be provided in the Statistical Analysis Plan.

The CGI-TS-S endpoints currently listed as time-to-event exploratory endpoints may be considered as secondary endpoints, if there is a strong correlation between subjects meeting Relapse criteria based on YGTSS-TTS and those who also had at least a 1-point reduction on CGI-TS-S. The strong correlation would suggest Relapse is not a competing risk. Details will be provided in the Statistical Analysis Plan.

The time-to-event estimand for the primary endpoint, which uses the mITT study population, and for the time-to-event secondary and exploratory endpoints related to Relapse will rely on a treatment policy strategy (which also has elements of a composite strategy, in that three intercurrent events, initiation of additional medications and hospitalization for worsening symptoms are incorporated as part of the definition of the primary endpoint). The intercurrent events of loss to follow-up will be assumed unrelated to treatment and treated in estimation as censored observations. Sensitivity analyses for the primary endpoint may assess alternate treatment of such missing data; details will be provided in the Statistical Analysis Plan.

The time-to-event endpoints not related to Relapse 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. Cause-specific Cox models will be used to obtain the hazard ratio and its 95% CI for time to worsening. In this model, subjects who complete or discontinue from the double-blind randomized withdrawal period before meeting endpoint criteria and for reasons not related to Relapse will be censored at the time of discontinuation. In addition, we will consider graphical and descriptive approaches in correlating the YGTSS with other scores (e.g., CGI-TS-S) in the study subjects acros time points.

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 multiple imput d using similar subjects (relevant demographic/baseline characteristics) from the placebo arm. For exploratory endpoints of mean change to fixed time point, additional analyses will be performed by time point.

In consideration of missing data, additional multiple imputation or tipping point methods may be used as a sensitivity analysis, such as:

- Missing at Random (MAR) predictive mean matching multiple imputation method
- Missing not at Random (MNAR) “jump to reference” multiple imputation method
- Tipping point analysis under MNAR assumption
- The mean change from Baseline (Day 1) to Week 12 (open-label) in YGTSS-TTS will be calculated. The paired t-test will be used for analyzing the change from baseline within treatment.
- The percentage of subjects with a 25% or greater decrease in their YGTSS-TS will be analyzed using Fisher Exact test.
- A fixed-sequence statistical strategy will be used to test selected efficacy endpoints in a predefined rank order hierarchy which will be outlined in the SAP.

The full details will be specified in the SAP.

Subgroup analyses will be conducted on all efficacy endpoints for the following populations:

- Children (≥ 6 and < 12 years of age), Adolescents (≥ 12 and < 18 years of age), and Adults (≥ 18 years of age).
- Subjects per region
- Males and Females
- Ethnicity and Race

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)

The treatment of missing data and sensitivity analyses for the endpoints will be specified in the Statistical Analysis Plan.

13.4.2. Safety Analysis

All safety data will be summarized in Safety population 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, vital signs, physical examination, and ECG data will be summarized by treatment and visit.

The Columbia-Suicide Severity Rating Scale (C-SSRS), 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 Self Report: Short Version (CAARS-S:S) and the Yale-Brown Obsessive-Compulsive Scale-II (Y-BOCS-II) will also be summarized descriptively.

13.4.3. Pharmacokinetics Analysis

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.

13.5. Sample Size Justifications

The planned number of Relapse events for the double-blind R/WD Phase is 49 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 expected to have occurred. The number of Relapses 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 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 rate in the open-label Stabilization Period is 50%. In addition, approximately 40 adult subjects are also expected to be enrolled.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, the Sponsor or its representatives will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities about protocol adherence, and the responsibilities of Emalex or its representatives. This will be documented in a Clinical Study Agreement between Emalex and the investigator.

During the study, a monitor from the Sponsor or its representatives will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report f rms, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Emalex.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor or its representatives and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of the Sponsor or its representatives, a regulatory authority, an Independent Ethics Committee, or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an Emalex audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact the Sponsor or its representatives immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

IRB/IEC approval for the investigation must be obtained prior to initial dosing of any subjects. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator shall make accurate and adequate written progress reports to the IRB/IEC at appropriate intervals, not exceeding one year. The Investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit within one year after last subject out (LPO) or termination of the study.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor or its designee may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

The Sponsor or its designee will implement and maintain quality assurance and quality control systems with written SOPs to ensure that studies are conducted, and data are generated, documented (record), and reported in compliance with the Protocol, GCP, and applicable regulatory requirement(s).

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Forms, must be approved, or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to the Sponsor or its representatives before he or she can enroll any subject/subject into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the Protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising and materials used to recruit and retain subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor or its designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (please see Appendices) and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

16.3. Written Informed Consent

The Principal Investigator(s) at ea h center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that hey are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

For subjects <18 years of age at Baseline, the parents', or legal guardian's signed and dated informed consent and the subject's signed and dated assent form must be obtained before conducting any study procedures. Subject assents will be administered according to the requirements of the site's IRB/IEC. Subjects ≥18 years of age must execute a written informed consent.

The Principal Investigator(s) must maintain the original, signed informed consent form and assent form. A copy of the signed informed consent form and assent form must be given to the subject and his/her parents or legal guardian.

16.4. Subject Diversity

Study centers will be selected in support of recruitment of an ethnically diverse group of study participants.

A review of the published literature indicated that while the prevalence of TD is greater in males as compared to females (Section 5.1) it does not show any disproportionate impact on specific ethnic groups. Hence the goal of participant recruitment would be to enroll a study population similar to the general population.

Study design, protocol inclusion/exclusion criteria and prohibited medications have been reviewed to ensure that they do not unduly restrict inclusion of any ethnic group. Study sites will be selected to ensure that sites are distributed across regions and are not confined to some regions of the country.

Sites that indicate potential to enroll a diverse population will be recruited for participation in the trial. Support for enrollment of disadvantaged population such as reimbursement for travel, parking assistance and other assistance as needed will be provided. Recruitment plans will include focus on enrolling study participants similar to the general population. Enrollment will be actively monitored so adjustments may be made on ongoing basis to assist in achieving the goal of subject diversity.

16.5. Subject Confidentiality and Data Security

The safety of the persons participating in the clinical trial and the validity of the data collected in the clinical trial are of the highest priority. The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is strictly prohibited. Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her medical welfare.

The Sponsor will use the information obtained during the conduct of this study for the development of ecopipam. The study Investigator is obliged to provide the Sponsor with complete test results and all data developed in this study.

In the event of a data security breach, Emalex as a data controller has implemented privacy and security controls designed to help protect subject personal data; including information security controls, firewalls, incident detection, and secure transfer measures. In the event of any accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data ("breach"), the controller has implemented procedures and measures to promptly address and mitigate any risk to the data. Emalex uses proactive and reactive detection channels to identify potential breaches. In the event of a breach, the data controller will notify the appropriate regulatory authorities and/or the subject in accordance with applicable data protection law.

Collected study data will be pseudonymized and maintained in a secure system. Such data will be processed and transferred using systems with proper certification and validation to ensure data security, privacy and quality management are in place. Technical and organizational measures to safeguard data include antivirus protection, encryption, data loss prevention practices, data privacy policy, password management policies, and access control. Additionally, a data protection officer (DPO) has been appointed by the Sponsor. Appropriate records of data processing activity are to be kept and the DPO will assist in case of a data breach, in which case the incident will be recorded, and notification will be made to the relevant Supervisory Authorities and data subjects, as applicable.

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and competent authority in each participating country, as well as that of any other applicable agency(ies), will be granted direct access to the subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

16.6. Ethnicity Data Collection

Ethnicity data will be collected for all subjects. In vitro metabolism studies with ecopipam and its active metabolite, N-desmethylecopipam revealed the primary route of metabolism to be through UGT and CYP enzymes, specifically UGT1A9 and CYP3A4. Ethnicity information collected in patients along with the pharmacokinetic sampling and analyses may help describe variability in exposures and response to ecopipam. Data from the Phase 2b EBS-101-CL-001 study along with Phase 3 study data across all ethnicities will provide information to support the exploration of exposure-response relationships and modeling and eventual dosing recommendations.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of time after the last marketing application approval, or if not approved period of time following the discontinuance of the test article for investigation based on country and local regulations. If it becomes necessary for Emalex or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records

18. PUBLICATION POLICY

The Principal Investigator is obliged to provide the sponsor with complete data derived from the program. During the program, only Emalex Biosciences may make information available to other participating physicians or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the Clinical Site Agreement, any public disclosure (including publicly accessible websites) related to the protocol or program results, is the sole responsibility of Emalex Biosciences.

Emalex Biosciences may publish any data and information from the program (including data and information generated by the physicians) without the consent of the treating physician. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Site Agreement. In the event of any discrepancy between the protocol and the Clinical Site Agreement, the Clinical Site Agreement will prevail. All scientific publications generated by Emalex Biosciences and its agents will be consistent with the principals outlined in Good Publication Practices.

Data from all sites participating in the program will be pooled and analyzed by Emalex Biosciences or its designees. The first publication of the results shall be made in conjunction with the results from other sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the program at all sites, the treating physician may publish or present the results generated at his or her site.

The treating physician will provide Emalex Biosciences with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. Emalex Biosciences shall inform the investigator in writing of any changes or deletions in such presentation or publi ation required to protect Emalex Biosciences' confidential and proprietary techni al information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the physician may proceed with the presentation or submission for publication unless Emalex Biosciences has notified the institution or the physician in writing that such proposed publication or presentation discloses Emalex Biosciences' confidential and proprietary technical information. Further, upon the request of Emalex Biosciences, the physician will delay the publication or presentation for an additional 90 days to permit Emalex Biosciences to take necessary actions to protect its intellectual property interests.

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20. WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the subject s best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of subjects, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on subjects or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their subjects in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the subjects who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declara ion have been addressed. The protocol should include information regarding funding, sponsors, insti utional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a conseq enc of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious subjects, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the subject which aspects of their care are related to the research. The refusal of a subject to participate in a study or the subject's decision to withdraw from the study must never adversely affect the subject-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the us of placebo, or no intervention, is acceptable; or

Where for compelling and sci ntifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the subjects who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual subject, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the subject or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available

21. CONTRACEPTION GUIDELINES

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical studies include the use of highly effective forms of birth control. These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized male partner
  - Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence (defined as r fraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).
  - In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence need to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

Adapted from: Clinical Trials Facilitation Group (CTFG). Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials. September 15, 2014.

Available at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

22. ALLOWABLE MEDICATIONS LIST FOR COMORBID CONDITIONS

The following medications are allowed for the treatment of subjects with ADHD, anxiety, depression, and OCD if doses have been stable for at least 4 weeks prior to Screening and the dose is constant during the study:

Stimulants for ADHD

- Amphetamine
- Amphetamine and dextroamphetamine
- Dexamphetamine
- Dexmethylphenidate
- Lisdexamfetamine
- Methylphenidate

Anti-Depressants

- Citalopram
- Desvenlafaxine
- Escitalopram
- Fluvoxamine
- Levomilnacipran
- Milnacipran
- Sertraline

Anxiolytics

- Lorazepam- Chronic use only
- Hydroxyzine

23. PROHIBITED MEDICATIONS LIST

Examples of prohibited medications in this section are provided below.

This is not a complete list. Please contact the Medical Monitor if you have questions about prohibited medications.

In general, medications that are prohibited fall into the following categories:

- Other medications used to treat tics associated with Tourette's disorder are prohibited.
- Medications that deplete dopamine to a significant extent (i.e., D2 receptor antagonists) or increase dopamine (i.e., dopamine agonists) to a significant extent are prohibited.
- Medications that have unfavorable drug-drug interactions with ecopipam that could have safety implications due to:
    - Increased exposure to the concomitant drug (i.e ecopipam is a strong inhibitor of CYP2D6 and substantially increases plasma levels of drugs that are metabolized by this system).
    - Increased exposure to ecopipam (i.e., ecopipam is primarily metabolized by UGT1A9 and inhibitors of this system and other UGT enzymes increases plasma levels of ecopipam up to 2x normal levels).
    - Decreased exposure to concomitant drugs with narrow therapeutic indices, anticancer drugs, anticoagulants, and/or antibiotic or antiviral drugs that require a minimum plasma level to mitigate dr g resistance unless routine monitoring of serum drug levels is performed (i.e. ecopipam moderately induces the metabolism of drugs metabolized by CYP2C CYP3A4, and or PGP substrates resulting in lower plasma levels of drugs that are metabolized by these systems).
    - Decreased exposure to ecopipam due to co-administration with strong inducers, leading to sub-therapeutic effect.
- Medications that are not appropriate for the pediatric population based on safety considerations.
- Investigational medications.

Some of the medications prohibited in this double-blind study may be allowed with dose adjustments in the open-label safety extension. Refer to Protocol EBS-101-TD-391.

Prohibited: Medications for the Treatment of Tics	
Amisulpride	Olanzapine
Aripiprazole	Pimozide
Asenapine	Quetiapine
Baclofen	Reserpine
Botulinum toxin	Risperidone
Clonazepam	Sulpiride
Clonidine	Tiapride
Duetetrabenazine	Tetrabenazine
Fluphenazine	Topiramate
Guanfacine	Valbenazine
Haloperidol	Ziprasidone

Prohibited: Anti-ADHD, Anti-Anxiety, Anti Depressant, and Anti-Psychotic Medications (not appearing on previous list)	
Alprazolam	Imipramine
Amoxapine	Loxapine
Amitriptyline	Maprotiline
Atomoxetine	Nortriptyline
Bupropion	Paliperidone
Chlorpromazine	Paroxetine
Clomipramine	Perphenazine
Desipramine	Propranolol
Doxepin	Protriptyline
Dronedarone	Thioridazine
Droperidol	Trimipramine
Duloxetine	Venlafaxine
Fluoxetine	Viloxazine

Prohibited: Medications that Significantly Decrease Dopamine Levels (not appearing on previous lists)	
Chloroethylnorapomorphine	Domperidone
Cinnarizine	Metoclopramide

Prohibited: Medications that Significantly Increase Dopamine Levels (not appearing on previous lists)	
Apomorphine	Pramipexole
Bromocriptine	Ropinirole
Cabergoline	Rotigotine

Prohibited: Sensitive CYP2D6 Substrates (not appearing on previous lists)	
Codeine	Prajmaline
Dextromethorphan	Propafenone
Eliglustat	Repinotan (IV)
Encainide	Tamoxifen
Enclomiphene	Tolperisone
Ibogaine	Tolterodine
Metoprolol	Tramadol
Methoxyphenamine	Traxoprodil
Nebivolol	Trimipramine
Nicergoline	Tropisetron
Perhexiline	Vernakalant

Prohibited: UGT Inhibitors **(not appearing on previous lists)**	
Mefanamic acid	Propofol
Mycophenolic acid	Valproic acid

Prohibited: Sensitive CYP3A4 and CYP2C19 Substrates- Prohibited unless routine monitoring of serum drug levels is performed **(not appearing on previous lists)**	
Amiodarone	Macrolide antibiotics (Azithromycin, Erythromycin, Clarithromycin, etc.) for long term use
Anticoagulants (Apixaban, Rivaroxaban, Warfarin)	Paclitaxel
Antiretrovirals (Etravirine, Nelfinavir, Protease inhibitors)	Quinidine
Bortezomib	Sirolimus
Clopidogrel	Tacrolimus
Copanlisib	Thalidomide
Cyclophosphamide	Ticagrelor
Cyclosporine	Tyrosine kinase inhibitors (Ivosidenib, Lapatinib, Larotrectinib Nintedanib, etc.)
Docetaxel	Vinblastine
Dronedarone	Vincristine
Lidocaine (IV only, topical allowed)	

Prohibited: PGP Substrates- Prohibited unless routine monitoring of serum drug levels is performed **(not appearing on previous lists)**			
Acalabrutinib	Edoxaban	Irinotecan	Rivaroxaban
Albendazole	Elbasvir	Ledipasvir	Proguanil
Apixaban	Emtricitabine	Linezolid	Saquinavir
Bictegravir	Erlotinib	Maraviroc	Simeprevir

Prohibited: PGP Substrates- Prohibited unless routine monitoring of serum drug levels is performed **(not appearing on previous lists)**			
Dabigatran	Etoposide	Mitoxantrone	Sofosbuvir
Dicloxacillin	Everolimus	Nevirapine	Tenofovir
Digoxin	Glecaprevir	Paritaprevir	Velpatasvir
Doravirine	Idarubicin	Pazopanib	Venetoclax
Doxorubicin	Indinavir	Pibrentasvir	

Prohibited: Strong Inducers of Drug Metabolism **(not appearing on previous lists)**	
Apalutamide	Mitotan
Avasimibe	Rifampin
Enzalutamide	Rifapentine
Ivosidenib	St John's Wort extract
Lumacaftor	

Prohibited: Not Appropriate for Pediatric Patient Population **(not appearing on previous lists**	
Monoamine oxidase inhibitors (MAOIs)	

24. DISALLOWED CONCOMITANT MEDICATION TIME-FRAMES

Disallowed for 6 Months Prior to Screening	
Abilify Maintena	Haloperidol decanoate
Aristada	Paliperidone palmitate
Botulinum toxin	

Disallowed for 3 Months Prior to Screening	
Fluphenazine decanoate	Zuclopenthixol decanoate
Risperidone microspheres	Zyprexa Relprevv

Disallowed for 4 Weeks Prior to Screening	
All Investigational Medications	Risperidone
Aripiprazole	Itopride
Chloroethylnorapomorphine	Loxapine
Chlorpromazine	Metoclopramide
Cinnarizine	Paliperidone
Desmethoxyfallypride	Perphenazine
Domperidone	Pimozide
Eticlopride	Quetiapine
Fallypride	Reserpine
Fluoxetine	Thioridazine
Haloperidol	Ziprasidone

Disallowed for 14 Days Prior to Baseline	
Baclofen	Guanfacine
Clonazepam	Tetrabenazine
Clonidine	Valbenazine
Duetetrabenazine	