ECOPIPAM (EBS-101)
EBS-101-COFD-201

IND Number: 128278

Protocol Number: EBS-101-COFD-201

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Exploratory Study to Evaluate the Efficacy and Safety of Ecopipam Tablets in Adults with Childhood Onset Fluency Disorder (Stuttering)

Indication Studied: Adult Subjects with Childhood Onset Fluency Disorder (Stuttering)

Protocol Version/Date: 4.0 / July 16, 2021

Sponsor Address: Emalex Biosciences, Inc.
330 N Wabash Ave, Suite 3500
Chicago, IL 60611

1. PROTOCOL HISTORY OF CHANGES

Protocol Version	Protocol Date
2.0	April 24, 2020
3.0	September 21, 2020
4.0	July 16, 2021

Major changes from protocol version 3.0 to 4.0 were made in the sections below and the relevant sections in the synopsis:

Section	Revision/Addition	Reason for Revision/Addition
Synopsis # of study centers and studied period	Added a 9th study center and updated the estimated date last subject completed to Q1 2022.	Slower enrollment than expected due to site disruptions during COVID-19 restrictions.
8.1 inclusion criterion #5	Males and females presenting with a history of stuttering for at least 2 years with onset prior to age ≥ 8 ~~years~~.	Implemented as per Protocol Clarification Memo #1
8.1 inclusion criterion #11	Added: Females are considered not to be of childbearing potential if they are either postmenopausal (amenorrhea for at least 2 years after the age of 42); or permanently sterilized (e.g., documented bilateral tubal ligation, hysterectomy, bilateral salpingo-oophorectomy, bilateral oophorectomy, etc.) for 6 months minimum prior to Visit 1.	Definition of women of childbearing potential added for clarity

Section	Revision/Addition	Reason for Revision/Addition
8.1 inclusion criterion #12	Sexually active male subjects must use a double barrier method of contraception **with their partner of childbearing potential** during the study and agree to continue the use of male contraception for at least 30 days after the last dose of study drug.	Implemented as per Protocol Clarification Memo #2
8.3 Subject Withdrawal, Removal, and Replacement Criteria	Added instructions when to dispense the taper down kit and when to discontinue subjects who do not adhere to the study treatment regimen.	Added for consistency with the Emalex Study Drug Handling Manual.
10.4 Study Drug Provisions 10.7 Study Drug Accountability 10.8 Study Drug Handling and Disposal Table 3 Schedule of Assessments, footnote h	Added clarification that a responsible person to manage/handle study drug may be delegated the activity in lieu of a pharmacist across multiple protocol sections.	No compounding or special handling by a pharmacist is required for the study drug. The Investigator must delegate study drug management/handling to a responsible person.
11.2 Secondary Efficacy Assessments	The Change from Baseline in the SSS score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to Week 12 is moved to a key secondary endpoint	The SSS replaces the OASES as a key secondary endpoint of patient-reported outcomes in the testing hierarchy. The subject must answer 100 questions in the OASES which may lead to subject fatigue and insufficient attention to responses. The SSS on the other hand consists of 8 items and is hence anticipated to be completed with lesser likelihood of subject fatigue.

Section	Revision/Addition	Reason for Revision/Addition
12.1.1.6 Central Laboratory Tests	Added clarification that subjects should be fasting for all blood laboratory tests following Visit 1 screening	Subjects are consented at Visit 1 screening and therefore, not instructed to fast prior to Visit 1.
12.2.1.3 Adverse Events of Special Interest (AESI)	Created an independent section for AESI and added the following AEs: weight gain, extrapyramidal symptoms, **convulsions, depression and suicide/self injury, drug abuse, drug dependence, drug withdrawal, dyslipidemia, hepatic disorders, hyperglycemia/new onset diabetes mellitus, neuroleptic malignant syndrome, parkinsonism, and psychosis/psychotic disorders.**	A priori defining adverse events of special interests to characterize ecopipam
7.1 Overall Study Design Table 3 Schedule of Assessments, footnote d 11.1.1.1 Stuttering Severity Instrument – Fourth Edition (SSI-4) Interview and Scoring	Added specifications to the SSI-4 interview expectations for clarity across multiple protocol sections: The subject and interviewer are in separate locations using a device provided by the qualified vendor. Every attempt should be made to perform this assessment by the same SSI-4 interviewer at the same time and same location at each visit. All SSI-4 interviews are conducted via video recording.	Details of the SSI-4 interview are added.
10.1 Study Drug	Added information that the details of study drug handling are provided in	To reference the companion Emalex Study Drug Handling Manual.

Section	Revision/Addition	Reason for Revision/Addition
	detail in the Emalex Study Drug Handling Manual	
13.1 Analysis Population	Added the expectation that the Modified Intention-to-Treat (mITT) population will include all randomized subjects who received at least one dose of study drug **and have at least one post-baseline efficacy evaluation completed.**	Edited for consistency with the Statistical Analysis Plan.

PROTOCOL SIGNATURE PAGE

This protocol has been approved by the Medical Officer:

07/20/2021

Atul R. Mahableshwarkar, MD, DFAPA **Date**
Emalex Biosciences, Inc.
Chief Medical Officer and Senior Vice President, Drug Development

Principal Investigator Declaration:

I have read and understood the requirements and conditions of the study protocol. I am aware of my responsibilities as an Investigator under the guidelines of the Internal Conference on Harmonization Good Clinical Practice (ICH GCP E6) standards, the Declaration of Helsinki, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the study team assigned to me who will be involved in the study.

I agree to use the study material, including investigational treatment study drug, only as specified in the protocol.

I understand that the protocol must be approved by the Ethics Committee and Regulatory Authorities prior to its implementation. I confirm that if I or any of my staff are members of the ethical review board, we will abstain from deliberation and voting on this protocol.

I understand that non-compliance with the study protocol may lead to early termination of the study.

Principal Investigator Signature **Date**

Principal Investigator Printed Name _____

2. SYNOPSIS

Name of Sponsor/Company:
Emalex Biosciences, Inc.

Name of Investigational Product:
Ecopipam Tablets

Protocol Number: EBS-101-COFD-201

Title of Study:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Exploratory Study to Evaluate the Efficacy and Safety of Ecopipam Tablets in Adults with Childhood Onset Fluency Disorder (Stuttering)

Study center(s): Approximately 9 sites in the United States

Studied period (years):	**Phase of development:**
Estimated date first subject enrolled: Q3 2020 Estimated date last subject completed: Q1 2022	2

Objectives:

Primary

The primary objective of this study is to evaluate the efficacy of ecopipam tablets in adult subjects (≥ 18 years of age) with childhood onset fluency disorder.

Secondary

The secondary objectives of this study are to evaluate the safety of ecopipam tablets in adult subjects (≥ 18 years of age) with childhood onset fluency disorder and to characterize the pharmacokinetics (PK) of ecopipam and its active metabolite (EBS-101-40853) after oral administration of ecopipam tablets in this patient population.

Exploratory

To evaluate the potential PK/pharmacodynamic relationship between plasma levels of ecopipam and EBS-101-40853 and safety and/or treatment effect, if possible.

Methodology:

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 exploratory study in adult subjects (aged ≥ 18 to years) with childhood onset fluency disorder (stuttering).

Following a 28-day Screening period and approval by a Central Enrollment Committee (CEC) which will confirm a subject's conformance with protocol eligibility criteria as well as ensure suitability, subjects will proceed to the Baseline visit. At the Baseline visit, eligible subjects will be randomized 1:1, stratified by weight band to receive either a target steady-state ecopipam HCl dose of ~2 mg/kg/day or matching placebo for a 12-week Treatment Period consisting of a 4-week Titration Phase followed by an 8-week Maintenance Phase.

Subjects will return to the clinic at Weeks 4, 8 and 12 and for follow-up at days 7 and 14 after study completion or early termination. Adverse events and other safety parameters will be assessed by phone or video conference at Weeks 2, 6 and 10, and 30 days after the last study drug administration. Signs or symptoms of withdrawal, abuse, and dependence will be monitored throughout the study.

At the end of the Treatment Period or Early Discontinuation, subjects will taper study drug by 25 mg/day until off study drug, for up to 1 week.

Where possible, safety and efficacy assessments will be made available for remote administration in the case that restrictions as a consequence of COVID-19 or other natural disaster prevent in clinic study visits. Blood samples for pharmacokinetics intended at Weeks 4 and 12 will not be considered protocol deviations if missed due to these restrictions.

Sample Size Justification:

A sample size of 68 subjects (34 subjects per treatment arm) will provide ≥80% power to detect a 20% difference on the SSI-4 between ecopipam and placebo groups on change from Baseline to Week 12, with standard deviation = 24.7 and alpha = 0.05, assuming 10% drop out.

Number of subjects (planned): Approximately 34 per arm; Approximately 68 total

Eligibility Criteria:

Inclusion Criteria

1. Subject must be able to read and write in English and provide written informed consent.
2. Subjects must be ≥ 18 years of age at time of screening.
3. Subjects must weigh ≥ 45 kg (~ 99 lbs).
4. Subjects must satisfy DSM-5 criteria for childhood onset fluency disorder (stuttering).
5. Males and females presenting with a history of stuttering for at least 2 years with onset prior to age 8.
6. Stuttering must be developmental in nature.
7. Stuttering severity, scored by a central rater, must be of at least moderate severity on the SSI-4 at Screening and Baseline.
8. Subjects must have completed an adequate course of speech therapy as determined by the Investigator.
9. Subjects must have a qualifying IOS or Android smartphone to complete study assessments remotely, when applicable due to COVID-19 restrictions or other natural disaster.
10. Subjects must be off all medications used to treat stuttering for at least 3 months prior to Screening.
11. Females of childbearing potential who are sexually active must be using double barrier method (condom and IUD, condom and spermicide, etc.) in addition to any oral contraceptive they may be using and agree to continue use of double-barrier contraception for the duration of their participation in the study. They must also agree to use double-barrier contraception for 30 days after their last dose of study drug.

    Females are considered not to be of childbearing potential if they are either postmenopausal (amenorrhea for at least 2 years after the age of 42); or permanently sterilized (e.g., documented bilateral tubal ligation, hysterectomy, bilateral salpingo-oophorectomy, bilateral oophorectomy, etc.) for 6 months prior to Visit 1.
12. Sexually active male subjects must use a double barrier method of contraception with their partner of childbearing potential during the study and agree to continue the use of male contraception for at least 30 days after the last dose of study drug.
13. Subjects must be initially approved by a Central Enrollment Committee prior to Baseline.

Exclusion Criteria

1. Stuttering related to a known neurological cause of stuttering (e.g. head trauma, stroke, etc.).
2. Subjects who have initiated new behavioral therapies for stuttering fewer than 10 weeks prior to Baseline.

3. Subjects who have unstable medical illness or clinically significant abnormalities on laboratory tests or ECG at Screening.
4. Subjects with a significant risk of committing suicide based on history, routine psychiatric status examination, Investigator's judgment, or who had an answer of ''yes'' to either of questions 4 or 5 (currently or within the past 30 days) on the Baseline/Screening version of the Columbia Suicide Severity Rating Scale (C-SSRS).
5. Subjects who are currently pregnant or lactating.
6. Subjects who have moderate to severe renal insufficiency at Screening (eGFR < 60 mL/min/1.73m^2).
7. Subjects who have hepatic insufficiency at Screening
8. Subjects with current or recent history of DSM-5 substance use disorder (with the exception of nicotine) within 3 months from Screening.
9. Subjects with positive urine drug screen (cocaine, amphetamine, methamphetamine, tetrahydrocannabinol (THC), benzodiazepines, barbiturates, phencyclidine (PCP), or opiates at Screening or Baseline.
10. Subjects with a lifetime history of a major depressive episode.
11. Subjects with a history of attempted suicide < 1 year from Screening.
12. Subjects with a Patient Health Questionnaire-9 (PHQ-9) score ≥10 at Screening or Baseline.
13. Subjects with a history of seizures (subjects whose only seizures were febrile seizures that occurred >2 years ago may be enrolled).
14. Subjects with a myocardial infarction within 6 months from Screening.
15. Subjects who have a clinically significant abnormal 12-lead ECG Screening or Baseline (mean QT interval of >450 msec in males or >470 msec in females).
16. Subjects who have had previous treatment with ecopipam.
17. Subjects who have known allergies which exclude them from taking ecopipam tablets.
18. Subjects who have had previous treatment with an investigational study drug within 3 months of Screening.
19. Subjects receiving psychostimulants, such as amphetamines.
20. Subjects receiving anti-anxiety, anti-depressant, anti-psychotic, or anti-ADHD medications within 3 months of Screening.
21. Subjects who have a need for medications which would have unfavorable interactions with ecopipam, e.g., dopamine antagonists or agonists (including bupropion), tetrabenazine, monoamine oxidase inhibitors, or St. John's Wort.
22. Subjects who are unable to swallow tablets.
23. Any subject who in the opinion of the investigator is unsuitable for the study.

Investigational product, dosage and mode of administration:

Ecopipam HCl 12.5, 50, and 75 mg tablets; target dose of ~2 mg/kg/day; oral administration, once daily in evenings before bedtime.

Dosing will be stratified by the following weight bands to better achieve the target dose:

45 to ≤68 kg; 69 to ≤83 kg; and >83 kg.

A target dose of ecopipam HCl ~2 mg/kg/day or matching placebo will be administered during the 4-week Titration Phase and the 8-week Maintenance Phase for each of the weight bands:

Weight (kg)	TREATMENT PERIOD				
	Titration Phase				Maintenance Phase
	Dose (mg) Week #1	Dose (mg) Week #2	Dose (mg) Week #3	Dose (mg) Week #4	Dose (mg) Week #5 - 12
45 to ≤68	25 (2 × 12.5)	50	75	100 (2 x 50)	100 (2 x 50)
69 to ≤83	25 (2 × 12.5)	50	100 (2 x 50)	150 (2 × 75)	150 (2 × 75)
>83	25 (2 × 12.5)	50	100 (2 x 50)	200 (4 x 50)	200 (4 x 50)

All doses will be administered once daily in the evening at bedtime, except for in-clinic dosing at Visit 4.

At the end of the Treatment Period or Early Discontinuation, subjects will taper study drug by 25 mg/day until off study drug, for up to 1 week.

Duration of treatment:

The 12-week Treatment Period consists of a 4-week Titration Phase followed by an 8-week Maintenance Phase.

Subjects will complete 7 in-clinic visits and 5 visits by telephone and/or other means of remote assessment for a total of up to ~20 weeks (including up to 4 weeks of Screening).

Reference therapy, dosage and mode of administration:

Matching placebo tablets, oral administration, once daily in evenings at bedtime.

Criteria for Evaluation:

Efficacy:

Primary efficacy endpoint:

- Change in the Stuttering Severity Instrument 4th Edition (SSI-4) for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12 as measured by a central rater.

Key Secondary Endpoints:

- Change in the Subjective Screening of Stuttering (SSS) score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12.
- Change in the Clinical Global Impressions-Severity (CGI-S) score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12.

Other Secondary efficacy endpoints include:

- Change in the Overall Assessment of the Speaker's Experience of Stuttering (OASES) score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12
- Change in the Clinical Global Impressions-Improvement (CGI-I) score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12
- Change in the SSI-4 percentage of syllables stuttered for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to the end of therapy at Week 12
- Change in the SSI-4 frequency sub-score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to the end of therapy at Week 12

- Change in the SSI-4 duration sub-score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to the end of therapy at Week 12
- Change in the OASES Section IV score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12
- Changes in all primary and secondary endpoints for subjects receiving ecopipam at Weeks 4 and 8

Rank order of hierarchy of the primary, key secondary, and other secondary endpoints will be outlined in the Statistical Analysis Plan.

Safety:

Safety will be assessed by monitoring and recording all adverse events (AEs) and Serious Adverse Events (SAEs) (all visits), regular monitoring of hematology, blood chemistry, and urine values (Screening, Baseline, Week 12, and 7 and 14 day Follow-up visits). HbA1c will be measured at Baseline and Week 12. Regular measurement of vital signs (height, weight, orthostatic blood pressure and pulse) and an ECG will occur at Baseline and Weeks 4, 8 and 12, and 7 and 14 day Follow Up visits. A complete physical examination will be conducted at Baseline and Week 12, and a brief physical exam as necessary per PI judgment based on reported symptoms at all other clinic visits. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered at all visits except 30 day Follow Up visit. Additional safety outcomes (Baseline and Weeks 4, 8, and 12) will include the Public Health Questionnaire-9 (PHQ-9), the State-Trait Anxiety Inventory for Adults™ (STAI-AD), the Extra-pyramidal Symptom Rating Scale (ESRS). Signs or symptoms of withdrawal, abuse, and dependence will be monitored throughout the study.

Pharmacokinetic:

Blood samples will be collected to measure concentrations of ecopipam and its major (active) metabolite, EBS-101-40853 at Weeks 4 and 12.

Subjects will be instructed to withhold their at-home administration of study drug the evening prior to the Week 4 visit and record the last date and time of study drug administration. The Week 4 visit will be scheduled for a morning appointment. The study drug administration for this day will occur at the site under the supervision of the study investigator. An intravenous catheter will be placed, and the subject will have three PK blood samples collected at the following time points: 1) pre-dose (20 to 36 hrs since the last dose); and 2) post-dose between 0.5 and 1.5 hours; and 3) post-dose between 2 and 4 hours. Any samples should be collected at least 30 min apart.

At the Week 12 visit, a PK blood sample will be collected at the end of the visit with the actual time of sample collection. PK blood samples intended at Weeks 4 and 12 will not be considered protocol deviations if missed due to restrictions as a consequence of COVID-19 or other natural disaster.

Blood samples will be processed as outlined in the protocol and plasma will be frozen, shipped and analyzed for ecopipam and EBS-101-40853.

Statistical methods:

Efficacy:

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

The primary efficacy endpoint for this trial will be the change in the SSI-4 total score from Baseline to Week 12 for ecopipam compared with placebo from Baseline to end of treatment at Week 12, scored by a central rater.

The primary endpoint will be assessed with a Mixed Model for Repeated Measures (MMRM) which will include fixed effects for treatment, visit (categorical week in trial), interaction between treatment

and visit, center and a covariate for baseline score. Taking consideration of missing data, multiple imputation or tipping point method may be used as a sensitivity analysis. Additional analyses may need to be conducted for data not collected at sites and/or collected via remote administrations when visits are restricted due to consequences of COVID-19 or other natural disaster.

Secondary endpoints will be evaluated in a similar manner with hierarchy to preserve alpha.

The full details will be specified in the Statistical Analysis Plan.

Safety:

The safety population will include all randomized 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 analysis will be conducted and summarized in a separate report, using data from this study along with data across other clinical pharmacology 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.

Abbreviation	Explanation
ADHD	Attention Deficit/Hyperactivity Disorder
AE	Adverse event
AESI	Adverse Events of Special Interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
BARS	Barnes Akathisia Rating Scale
BUN	blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
CGI-I	Clinical Global Impressions-Improvement
CG1-S	Clinical Global Impressions-Severity
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
COVID-19	SARS-CoV-2 (coronavirus)
DIMD	Drug-Induced Movement Disorders
ECG	Echocardiogram
EDC	Electronic Data Capture
EEG	Electroencephalograms
ESRS	Extra-pyramidal Symptom Rating Scale
FDOPA	Flurodopa F-18 (FDOPA)
GCP	Good Clinical Practice
HbA1c	Hemoglobin
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous

Abbreviation	Explanation
IWRS	Interactive Web-based Randomization System
LDH	lactate dehydrogenase
LFT	Liver function tests
LND	Lesch-Nyhan Disease
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
MMRM	Mixed Model for Repeated Measures
NOAEL	No-Observable-Adverse-Effect Level
OAE	Other significant adverse event
OASES	Overall Assessment of the Speaker's Experience of Stuttering
PCP	Phencyclidine
PG	Pathological Gambling
PHQ-9	Public Health Questionnaire - 9
PI	Principal Investigator who leads the study conduct at an individual study center.
PK	Pharmacokinetics
PO	Per os/ given by mouth
PP	Per-Protocol population
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class
SSI-4	Stuttering Severity Instrument 4th Edition
SSS	Subjective Screening of Stuttering
STAI-AD	State-Trait Anxiety Inventory for Adults
TD	Tardive Dyskinesia
TEAE	Treatment Emergent Adverse Event
THC	Tetrahydrocannabinol
TS	Tourette Syndrome

5. INTRODUCTION

5.1. Background on Childhood Onset Fluency Disorder (Stuttering)

Childhood onset fluency disorder, also known as stuttering or stammering, is a common multifactorial speech disorder. It is normally seen with recurrent prolongations, reverberations, or blocks of sounds, syllables, phrases or words (Maguire et al, 2012). During these unintentional breaks in speech, the individual is not able to make sounds. The main issue of individuals with childhood onset fluency disorder is that of repetition. Some of the coping mechanisms are blocks and prolongations, which are used to mask repetition. Other characteristics of this disorder are word substitutions or unwarranted physical tension while trying to formulate speech (Maguire et al, 2012). Other simultaneous symptoms can include facial grimacing, tremors of muscles used in speech, and eye blinks in addition to the evasion of words or circumstances which aggravate stuttering episodes (Maguire et al, 2012).

Childhood onset fluency disorder remains the most frequent type of stuttering. A reported five percent of children are affected by this disorder, and approximately 80-90% of stuttering starts by about age six years of age (Maguire et al, 2012). About seventy five percent of these individuals ultimately recover (Maguire et al, 2012). This recovery is normally seen by about 16 years of age. Nevertheless, in many cases, stuttering continues into adulthood. Early diagnosis and treatment of childhood onset fluency disorder is a key to early recovery.

Stuttering can greatly impact an individual's social, occupational and academic functioning. There are no approved pharmacologic therapies for this condition. Current forms of speech therapy are focused on compensatory strategies which typically do not result in spontaneous fluency and requires conscious monitoring. As an effect, the speech may sound unnatural. The speech therapy methods are associated with high rates of relapse. Using electronic devices to improve speech fluency or cognitive behavioral therapy may also be effective.

5.2. Role of the Dopamine System in Childhood Onset Fluency Disorder

Much has been learned in recent years of the neurophysiology of stuttering. In a recent review of brain research on stuttering by Chang et al. (2018), it is argued that convergent findings "strongly suggest neural circuit level deficits that affect the planning and execution of self-initiated, intrinsically timed sound sequences." These circuits include white matter pathways to the vicinity of the posterior part of Broca's area (premotor), and basal ganglia-thalamocortical loops. It is quite possible that deficits of white matter connections to the speech premotor regions interact with an unstable and dysregulated basal ganglia function, making the voluntary control of the speech muscles unstable and vulnerable to the effects of interference, for example from cognitive or emotional stress.

The possible role of the dopamine system has been highlighted based on clinical experience with dopamine D2 receptor antagonists (risperidone and olanzapine) improving stuttering symptoms, but also based on imaging of the brain's dopamine system indicating elevated dopamine turnover in persons who stutter (Maguire et al, 2000; Maguire et al, 2002; Maguire et al, 2004; Maguire et al, 2004b; Wu et al, 1997). The functions of the basal ganglia and dopamine in relation stuttering were reviewed by Alm (2004). It is likely that the population of persons who stutter is heterogeneous in these regards, with subgroups with differing responses to dopaminergic drugs.

5.3. Rationale of Ecopipam Use in the Intended Patient Population

Ecopipam is a selective dopamine D1 receptor antagonist, which has shown effect for Tourette syndrome (TS) in a recent randomized, controlled clinical trial in subjects aged 7 to 17 years (Gilbert et al, 2018). Ecopipam reduced tics and was well tolerated at doses ~1.8 mg/kg/day (range from ~0.9 to 2.9 mg/kg/day). In particular, the participants did not show common side effects associated with D2 antagonists, such as weight gain or drug-induced movement disorders (DIMD). An open-label pilot study with ecopipam HCl (100 mg/day) for stuttering adults also showed promising results (Nelson et al, 2018). Five subjects completed the study, with a mean reduction of the SSI score for stuttering severity of 29%. In particular, the 4 out of 5 strongest responders showed an average reduction of 70% for the duration of the longest moments of stuttering. The results suggest a potential treatment effect in persons who stutter.

Considering the previous clinical experience of D2 antagonists improving stuttering, the positive effect of a D1 antagonist may appear surprising. The imaging study by Wu et al, 1997 indicated strongly elevated levels of Flurodopa F-18 (FDOPA) uptake in some persons who stutter, in turn indicating elevated levels of dopamine release in the synaptic cleft. In this scenario, it is possible that the dysregulation is not mainly caused by the D2 receptor but by the D1 receptor. Further, the D2 receptor has a dual role in the synapse, acting also as a presynaptic autoreceptor, regulating the release of dopamine. D2 antagonists can block these autoreceptors, which in turn may aggravate excessive release of dopamine. Because of the regulatory function of the D2 receptor, it is likely that pharmacological interventions with this target will have more widespread effects, including adverse effects. Conversely, interventions targeting the D1 receptor may have more specific effects. However, the level of complexity makes any mechanistic model speculative, and there is a need for empirical data.

This study will provide valuable insights into developing a viable treatment for the millions of individuals who stutter. Stuttering shares many similarities to TS in that both are related to abnormalities of the basal ganglia, begin in childhood, follow a waxing/waning course, made worse under anxiety or stress, and respond to dopamine antagonists. With such, ecopipam, with its dopaminergic mechanism holds promise as a viable treatment option for stuttering.

5.4. Ecopipam Background Data

5.4.1. Ecopipam Nonclinical Data

5.4.1.1. Toxicology

The nonclinical development program for ecopipam comprised studies of bioavailability, acute and repeated-dose toxicity (including oral [PO] gavage, 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 any enzyme induction or loss of efficacy or tolerance in animals. Ecopipam is not considered embryotoxic, fetotoxic, or teratogenic in rats at doses up to 162 mg/kg. In rabbits, the no-observable-adverse-effect level (NOAEL) for both maternal and developmental toxicity is > 150 mg/kg, but < 300 mg/kg. Ecopipam is not considered genotoxic or mutagenic. However,

ecopipam 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.

Results of nonclinical pharmacokinetic and metabolism studies showed that ecopipam is rapidly absorbed after oral dosing and, in rodents and monkeys, is rapidly 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 Brochure for more detailed information about the known benefits and risks of ecopipam.

5.4.2. Ecopipam Clinical Data

5.4.2.1. Safety Data from Phase 1 and Initial Completed Phase 2/3 Studies

The early clinical program for ecopipam conducted by Schering-Plough investigated the safety and effectiveness of ecopipam for the treatment of obesity, cocaine addiction and schizophrenia in adults. These comprised 30 Phase 1 studies; seven Phase 2 pilot studies, 5 in subjects with schizophrenia and 2 (including 1 extension study) in subjects with cocaine addiction; and 1 completed Phase 2 and 3 discontinued Phase 3 studies in subjects with a primary diagnosis of moderate to severe obesity.

The Phase 1 studies examined ecopipam's pharmacokinetics, pharmacodynamics, bioavailability, distribution, food-effects on absorption, interactions with other drugs, bioequivalence of different formulations, and various physiological effects in cocaine users, smokers, or healthy subjects. The results of these studies demonstrate that ecopipam was well-tolerated with no clinically significant changes in physical examinations, vital signs, electrocardiograms (ECGs), laboratory tests, electroencephalograms (EEGs), neurological examinations, or liver function tests (LFTs).

Most of the reported adverse events were mild to moderate in intensity. The most commonly reported adverse event in Phase 1 clinical studies was somnolence. Other commonly reported adverse events in Phase 1 clinical studies were headache, fatigue, nausea and insomnia.

In a Phase 2 study (C197-184), 279 subjects with cocaine dependence in three dose groups (10-, 25-, and 100 mg/day) were exposed to ecopipam for eight weeks in a placebo-controlled study. No differences in the reduction of cocaine use were demonstrated in favor of ecopipam compared with placebo. The most common adverse events reported among all subjects in the cocaine addiction studies were fatigue, headache, nausea, insomnia, and somnolence. Fatigue and somnolence appeared to be reported more often in subjects treated with ecopipam than placebo. Somnolence appeared to occur in a dose-related fashion, occurring in 28% (26/94), 31% (29/94), 43% (39/91), and 20% (19/93) of subjects treated with ecopipam HCl, 10, 25, and 100 mg/day, and placebo, respectively.

Five open-label safety, tolerability and Phase 2 studies of ecopipam in 56 subjects with schizophrenia were conducted. Subjects diagnosed with acute schizophrenia, schizophreniform disorder, or bipolar schizoaffective disorders were treated with ecopipam HCl up to a daily dose of 600 mg. The maximum duration of treatment was six weeks. Ecopipam, when administered to subjects with schizophrenia, did not demonstrate efficacy in these studies. The most commonly reported adverse events were somnolence (21%, 12/56), headache, nausea, vomiting and dizziness (each reported in 14%, 8/56 subjects), insomnia (9%, 5/56), dyspepsia (7%, 4/56), and anxiety (7%, 4/56).

In a Phase 2, double-blind, placebo-controlled study (C/I98-271), 185 subjects with a primary diagnosis of moderate to severe obesity were treated with ecopipam HCl (10, 30, or 100 mg PO, once per day) for 12 weeks. Subjects receiving ecopipam HCl showed a dose-dependent weight loss. The most commonly reported adverse events by subjects receiving ecopipam HCl were headache, 19% (36/185), viral infection, 19% (36/185), somnolence, 18% (34/185), insomnia, 9% (17/185), and nausea, 9% (16/185).

In three Phase 3, double-blind, placebo-controlled studies (P00359, P00396, and P00741), obese subjects including type 2 diabetic subjects were treated with ecopipam HCl (50 or 100 mg PO, QD) for 52 weeks. Subjects receiving ecopipam showed a dose-dependent weight loss. Phase 3 studies were discontinued because of unexpected psychiatric adverse events (ecopipam 31% vs. placebo 15%), including depression, anxiety, and suicidal ideation, thereby excluding its projected use in weight management. The most frequently reported adverse events in all Phase 3 obesity studies receiving ecopipam were upper respiratory tract infection, 30% (439 of 1482 subjects reporting), insomnia 17% (248/1482), headache, 16% (244/1482), depression, 16% (236/1482), somnolence, 15% (216/1482), fatigue, 15% (215/1482), anxiety, 14% (211/1482), pharyngitis, 9% (137/1482), back pain, 8% (114/1482), nausea, 7% (107/1482). The frequencies of insomnia, depression, somnolence and anxiety were about twice as frequent in subjects receiving ecopipam compared to placebo. The frequencies of upper respiratory tract infection, headache, fatigue, pharyngitis, back pain and nausea were similar in frequencies in subjects receiving ecopipam and placebo.

Following acquisition of ecopipam by Psyadon Pharmaceuticals from Schering-Plough, two Phase 1 studies, one study in Lesch-Nyhan Disease (LND) subjects aged ≥6 years old (PSY101) and pharmacokinetics of ecopipam controlled release capsules in male adult volunteers (PSY401), were completed.

One Phase 2a study in adult subjects with Pathological Gambling (PG) (PSY201) was also completed. In addition, a Phase 3, multicenter, randomized, double-blind, 3-period crossover study with an open-label extension in subjects with LND (≥ 6 years old) (PSY102) was discontinued before completion for financial (non-safety related) reasons.

In the Phase 1 LND study (PSY101), in which 4 of 5 subjects were children, the most commonly reported adverse events were sedation (3 subjects), dystonia (2 subjects) and nausea (2 subjects).

In a Phase 2a, single-blind (the subjects were blinded to treatment assignment), nonrandomized study, 28 subjects with PG (PSY201) received placebo (1-2 tablets/day orally depending on their urge to gamble) for 1 week and then ecopipam HCl (1-2 50 mg tablets/day orally depending on their urge to gamble) for 6 weeks. The most commonly reported adverse events (incidence ≥5%)

were drowsiness (11%), fatigue (11%), anxiety (11%), vomiting (11%), headache (7%), fever (7%), depression (7%) and rhinorrhea (7%).

A Phase 3 study (PSY102) of ecopipam for the treatment of self-injurious behaviors in LND subjects was conducted. A total of nine pediatric subjects were enrolled before the study was terminated for non-safety related reasons. Ecopipam HCl was administered at either 50 mg/day (<20 kg body weight) or 100 mg/day (>20 kg body weight). In the PSY102 LND study, one subject aged 10 years old experienced dystonia, swallowing difficulty and depressed mood which involved persistent or significant disability or incapacity. The same subject experienced renal calculus, dystonia and bronchospasm which involved persistent or significant disability or incapacity and was determined that these symptoms were not related to the study drug. Another subject aged 6 years old experienced dysphagia, somnolence and depressed mood which involved persistent or significant disability or incapacity and were assessed possibly related to the study drug. Since dystonia and dysphagia have not been seen previously in other study populations and because Lesch-Nyhan subjects have a genetic mutation known to impact dopaminergic systems, it is believed that these adverse events are uniquely seen in this population and are unlikely to occur in subjects without this disorder.

5.4.2.2. Safety Data from Completed Phase 2 Clinical Studies in TS Subjects

Two Phase 2 studies in subjects with TS have been completed.

Study PSY301

In a Phase 2a multicenter, open-label, nonrandomized study, 18 adult subjects with TS (PSY301) were given ecopipam HCl 50 mg for 2 weeks followed by 100 mg for 6 weeks. The most commonly reported adverse events (incidence≥20%) were sedation (33%), insomnia (33%), fatigue (33%), somnolence (28%), headache (22%), muscle twitching (22%) and anxiety (22%).

Study PSY302

In a Phase 2b multicenter, double blind, randomized, crossover study (PSY302), 40 children/ adolescents (ages 7-17 years) were given ecopipam HCl up to 50 mg/day (if <75 lbs) or 100 mg/day (if >75 lbs) for four weeks

A total of 149 TEAEs were reported in 35 of the 40 treated subjects (87.50%). There was one serious TEAE during placebo treatment and one TEAE resulting in dose withdrawn permanently during ecopipam treatment. No TEAE resulted in death. There were 20 subjects (50%) reporting TEAEs related to study drug during ecopipam treatment and 10 subjects (25%) during placebo treatment. Forty percent (40%) of TEAEs were mild and 37.50% were moderate. Subject 02-12 decreased the dosage due to fatigue at Day 1 after starting ecopipam. Subject 06-11 was discontinued from the study due to rash starting at Day 0 of the second treatment phase (ecopipam).

The most common TEAEs during ecopipam treatment were headache (6 of 40), upper abdominal pain (4 of 40), nausea (4 of 40), vomiting (4 of 40), insomnia (4 of 40) and somnolence (4 of 40). The most common TEAEs during placebo treatment were nasopharyngitis (5 of 40), headache (5 of 40), upper abdominal pain (4 of 40) and diarrhea (4 of 40). The most common related TEAEs during ecopipam treatment were nausea (4 of 40) and somnolence (4 of 40). The most common

related TEAEs during placebo treatment were headache (3 of 40), somnolence (2 of 40) and initial insomnia (2 of 40).

There was no evidence that administration of ecopipam affected weight, Children's Depression Inventory (CDI) scores, or C-SSRS in the subjects. There were no clinically significant lab abnormalities, changes in vital signs, ECG, or physical exam findings after ecopipam administration.

5.4.2.3. Efficacy and Safety from Completed University of California Riverside Phase 2a Clinical Study in Adults with Childhood Onset Fluency Disorder

An exploratory, single-center, uncontrolled, open-label clinical study was conducted by investigators at the University of California Riverside to examine the safety and efficacy of ecopipam in adults with moderate to very severe developmental stuttering (Maguire et al, 2019). This study was an A-B treatment efficacy design, where the isolated treatment condition (B) is a tolerated 8th week dose of ecopipam. There were eight weeks between Baseline (A) and (B), including 5 visits to the study center.

Ten male and female volunteers (ages 18– 65 years) were enrolled. They were selected based on the following criteria: those who reported that the onset of stuttering was prior to 10 years of age; those rated to be at "moderate severity" or greater on the Stuttering Severity Instrument (SSI-4); those rated to be at a 12 or lower on the Montgomery-Asberg Depression Rating Scale (MADRS); and those who could speak English. The following exclusion criteria were used: participants who were unable to voluntarily consent, those with known neurological bases for their stutter, those who reported unstable medical or psychiatric illness, those who reported active substance abuse within three months, or those with any illness that would require the concomitant use of a central nervous system active medication.

Potential participants underwent a thorough clinical screening with physical examination, vital signs, and laboratory testing. An audio/video-recorded SSI-4 was completed for clinical outcomes and to determine stuttering severity. The examiner conversed with the participant, collecting at least 900 syllables of spontaneous speech. The participant was rated on the following scales so that extra-pyramidal, Tardive Dyskinesia (TD) side effects, depression and suicidality could be assessed: Columbia-Suicide Severity Rating Scale (C-SSRS), MADRS, Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BARS) and Abnormal Involuntary Movement Scale (AIMS).

The 10 subjects who successfully completed Screening procedures were enrolled into the study at the Baseline visit. All Screening measures were repeated, and the subject was asked to complete two attitudinal stuttering scales, the Subjective Screening of Stuttering (SSS) and Overall Assessment of the Speaker's Experience of Stuttering (OASES). The subjects were dispensed 50 mg ecopipam HCl to be taken daily at bedtime for the first two weeks.

At Weeks 2, 4, and 8, all tests were repeated, subjects evaluated for tolerability and the dose of ecopipam HCl was increased to 100 mg nightly if the subject was tolerating this study drug well, and their Clinical Global Impression-Improvement (CGI-I) score suggested no improvement in their stuttering. If the subject reported that they could not tolerate 100 mg of ecopipam HCl after this visit, the dosage was reduced to 50 mg per day.

Of the 10 qualified subjects enrolled, 1 male subject withdrew consent and 2 subjects withdrew (a male reported an inability to commute to the center and a female preferred a previous medication). Two other subjects who qualified for the study were identical twin males, and the results will be presented with and without their data included. The total number of subjects were: n=7 adult males for Study I; n=5 adult males for Study II.

Table 1 shows the mean and standard deviation comparisons between A (Baseline) and B (tolerated dose of ecopipam after 8 week of treatment) conditions for each of seven measures of interest in order of size of the Cohen's *d* effect sizes for the 5 subjects who completed the study. Table 2 shows the severity ranking changes from Baseline on the Stuttering Severity Instrument (SSI-4; Riley, 2009). In terms of observed stuttering behaviors, Figure 1 shows the significant (n=5; W=+15; $p<0.05$) differences found between the A (Baseline) and B (tolerated dose of ecopipam after 8 weeks of treatment) conditions in %SS. Ecopipam was well tolerated with no reported adverse events including no signals for increased depression as noted on the MADRS or suicidal thoughts as noted on the C-SSRS. Furthermore, there were no adverse events noted on the SAS, BARS and AIMS.

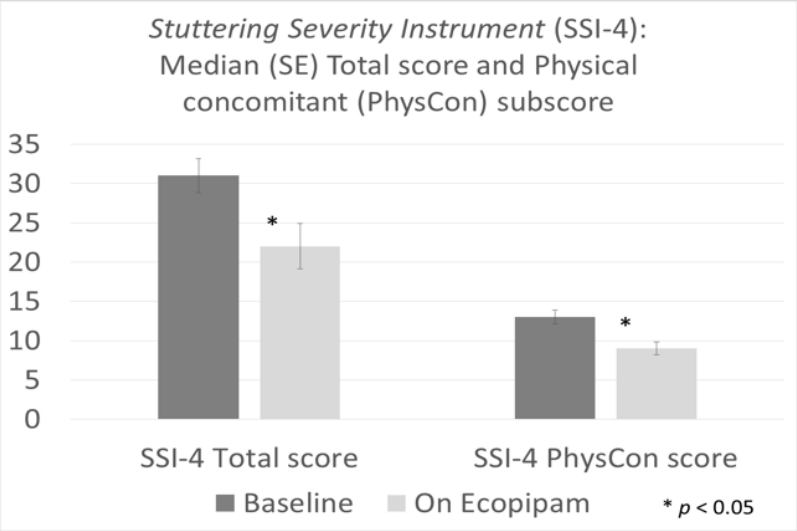
Table 1: The Mean (and standard deviation) for Each of Seven Measures in the A (Baseline) and B (Ecopipam) Condition is Ranked from Largest to Smallest Cohen's *d* Effect Size that was Computed

Measure	A (Baseline)	B (Ecopipam)	Cohen's *d*
1. OASES score	3.07 (0.31)	2.47 (0.31)	+1.918
2. SSS score	94.4 (28.6)	57.4 (25.9)	+1.358
3. SSI-4 score	35.4 (9.8)	26.4 (12.9)	+0.785
4. SSI-4 duration secs	10.4 (11.9)	4.3 (5.1)	+0.671
5. Reading rate in spm	106.6 (65)	137.6 (77)	-0.433
6. %SS-Speaking SSI-4	12.5 (9.2)	8.9 (9.8)	+0.379
7. %SS-Reading SSI-4	17.7 (11.7)	13.7 (9.8)	+0.370

Table 2: Stuttering Severity Instrument-4

Subj#	Baseline	End Of Study
#001	26 (mod.)	13 (v.mild)
#005	46 (v.sev.)	42 (v.sev.)
#007	31 (mod)	22 (mild)
#008	27 (mod)	17 (v.mild)
#010	46 (v.sev.)	38 (v.sev.)

Figure 1: Percent Syllables Stuttered (%SS) in *Stuttering Severity Instrument* Reading and Speaking



The investigators concluded that treatment with ecopipam was well-tolerated without adverse events. Participants with moderate stuttering made significant gains in overall stuttering severity as rated by the SSI-4, and the two participants with very severe stuttering showed minimal gains in overall severity. After 8 weeks of ecopipam therapy (B condition): (1) Fluency improved, reduced percent syllables stuttered in both reading and spontaneous speaking; (2) Reading completion was faster; (3) Stutter duration of the three longest stutters was shortest for those who tolerated ecopipam for 8 weeks (B condition); and (4) Scores on the OASES improved. However, interpretation of this data is limited given it was an open label study with no control group and the final analysis only included completers with no imputation for missing data from non-completers.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of ecopipam tablets in adult subjects with childhood onset fluency disorder.

6.2. Secondary Objectives

The secondary objectives of this study are to evaluate the safety of ecopipam tablets in adult subjects with childhood onset fluency disorder and to characterize the pharmacokinetics (PK) of ecopipam and EBS-101-40853 after oral administration of ecopipam in this patient population.

6.3. Exploratory Objectives

To evaluate the potential PK/pharmacodynamic relationship between plasma levels of ecopipam and its active metabolite and safety and/or treatment effect, if possible.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 exploratory study in adult subjects with childhood onset fluency disorder.

The SSI-4 will be administered by a dedicated site interviewer who is trained and certified by the Sponsor-approved rater training vendor. The dedicated SSI-4 site interviewer will not conduct any other study assessments nor interact further with the subject. This is intended to reduce the potential familiarity a subject may feel toward the administrator of the primary efficacy instrument.

Furthermore, centralized SSI-4 scoring is intended to reduce variability in scale scoring and increase standardized administration techniques through careful examination of all study visits. External, unbiased scoring of key project assessments will help to minimize the enrollment of ineligible subjects and improve the quality of the data while reducing variability in scoring. (Davidow & Scott, 2017).

One hundred percent of the administered SSI-4 interviews are conducted via video streaming and recorded using a device provided by the rater training vendor. Every attempt should be made, per subject, to perform the SSI-4 interview by the same SSI-4 interviewer, at the same time and same location at each visit.

The recorded SSI-4 interviews will be scored by central raters who are calibrated, expert clinicians.

Investigators will be informed of the central rater's scored assessment of stuttering severity at the Screening and Baseline visits for eligibility purposes. Thereafter, the SSI-4 scores from all relevant visits will be transferred to the Electronic Data Capture (EDC) system. The central rater scores will be used for all analyses.

The Central Enrollment Committee (CEC) has been developed as a quality measure to focus on ensuring inclusion/exclusion criteria and confirmation of diagnosis based on the comprehensive information gathered and verified by the Investigator. Subjects who receive CEC affirmation during the 28-day screening period may proceed to the Baseline visit.

At the Baseline visit, eligible subjects will be randomized 1:1 to receive either a target steady-state dose of ecopipam HCl ~2 mg/kg/day or matching placebo for a 12-week Treatment Period consisting of a 4-week Titration Phase followed by an 8-week Maintenance Phase.

Subjects will return to the clinic at 4, 8, and 12 weeks after Randomization and Follow-up visits 7 and 14 days after completing the Treatment Period or Early Discontinuation. Efficacy assessments will be conducted at Weeks 4, 8, and 12 and safety assessments will be conducted at all visits. Subjects will have adverse events and other safety parameters assessed by phone or video conference at Weeks 2, 6 and 10 and 30 days after the last study drug administration. Signs or symptoms of withdrawal, abuse, and dependence will be monitored throughout the study.

At the end of the Treatment Period or Early Discontinuation, subjects will taper study drug by 25 mg/day until off study drug, for up to 1 week.

Where possible, safety and efficacy assessments will be made available for remote administration in the case that restrictions, as a consequence of COVID-19 or other natural disaster, prevent in-clinic study visits. All SSI-4 interviews are conducted via video recording with the subject and interviewer in separate locations. Blood samples for pharmacokinetics intended at Weeks 4 and 12 will not be considered protocol deviations if missed due to these restrictions.

7.2. Number of Subjects

Approximately 68 subjects will be randomized in the study.

7.3. Treatment Assignment

Subjects will be randomized 1:1 to receive either ecopipam HCl ~2 mg/kg/day or matching placebo tablets.

7.4. Dose Stratification

Dosing will be stratified by the following weight bands to better achieve the ~2 mg/kg target dose: 45 to ≤68 kg, 69 to ≤83 kg, and > 83 kg. Those who cannot tolerate the target dose will be withdrawn from the study.

7.5. Criteria for Subject Study Discontinuation

A subject may elect to discontinue from the study at any time for any reason. All subjects who discontinue from the study will be reminded of the importance to complete the study drug Taper Phase and Early Termination assessments and encouraged to complete all Follow-up visits for safety.

A subject with a new positive response on questions 4 or 5 of the C-SSRS Since Last Visit version will be immediately discontinued from study drug and Investigator will perform suicide risk assessment. Dosing may be restarted at the discretion of the Investigator following consultation with the Sponsor or its designee.

Subjects will complete the PHQ-9 at Screening, Baseline and Weeks 4, 8, and 12. The qualified Investigator will review the completed form during the visit while the subject is available at the research site. A subject with a PHQ-9 score indicative of the onset of a new depressive episode at any visit will be assessed and may be discontinued from the study drug at the discretion of the Investigator. The Investigator will perform suicide risk assessment in subjects who respond positively to PHQ-9 question 9.

Subjects who discontinue early from the study will be evaluated for one of these primary reasons: AE, lost to follow-up, subject choice, inadequate therapeutic effect, restrictions due to COVID-19 or other natural disaster, 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.

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 officials from regulatory agencies discover conditions arising during the study that indicate that the study should be halted or that a study site should be closed, this action may be taken after appropriate consultation between the Sponsor and Principal Investigator. If the study is suspended or terminated, the Sponsor will ensure that applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate.

Table 3: Schedule of Assessments

Assessments are recommended to be conducted in an order for 1) least intrusive and earliest detection of screen fail criteria at Screening and Baseline visits; 2) prioritize fasting blood and urine collection early in the visit; 3) ensure that the subject breaks their fast prior to the SSI-4 interview and that the SSI-4 is completed early in the visit to preserve the integrity of the primary endpoint instrument; and 4) grouped for the convenience of patient reported outcomes and clinician outcome assessments. Please see the guidance document in the Investigator Site File binder.

Assessment[µ]	Screening	Baseline	Treatment Period					Taper Phase[#] Completion/ Early Termination	Follow-Up		Unscheduled[∞,]
			Titration Phase		Maintenance Phase				Day 7 & 14	Day 30	
Study Week	**Up to -4**	**0**	**2***	**4**	**6***	**8**	**10***	**12**	**13 & 14**	**16***	
Study Days	**Up to -28**	**1**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**91±3, 98±3**	**114±3**	
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 & 10**	**11**	
Informed Consent[a]	X										
Inclusion/ Exclusion	X	X									
Medical/Psychiatric/ Medication History	X	X									
CEC eligibility determination	X										
Randomization		X									
Physical Exam/Vital Signs[b]	X	X		X		X		X	X		X
Local ECG	X	X		X		X		X	X		X
Laboratory tests (Hematology, Chemistry and urinalysis)[c]	X	X		X		X		X	X		X
Urine Drug Screen	X	X						X			X

Assessment[µ]	Screening	Baseline	Treatment Period					Taper Phase[#] Completion/ Early Termination	Follow-Up		Unscheduled[∞,]
			Titration Phase		Maintenance Phase				Day 7 & 14	Day 30	
Study Week	**Up to -4**	**0**	**2***	**4**	**6***	**8**	**10***	**12**	**13 & 14**	**16***	
Study Days	**Up to -28**	**1**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**91±3, 98±3**	**114±3**	
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 & 10**	**11**	
Urine Pregnancy Test	X	X						X			X
DSM-5 Criteria for Stuttering checklist	X										
SSI-4[d]	X	X		X		X		X			X
CGI-S		X		X		X		X			X
CGI-I				X		X		X			X
SSS		X		X		X		X			
OASES		X		X		X		X			
C-SSRS	X	X	X	X	X	X	X	X	X		X
ESRS		X		X		X		X			
PHQ-9	X	X		X		X		X			X
STAI-AD		X[e]		X		X		X			X
PK Blood Draws				X[f]				X[g]			
Assess Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Assess Concomitant Medications	X	X		X	X	X		X	X		X
Dispense Study Drug[h]		X		X[f]		X		X			X

Assessment[µ]	Screening	Baseline	Treatment Period					Taper Phase[#] Completion/ Early Termination	Follow-Up		Unscheduled[∞,]
			Titration Phase		Maintenance Phase				Day 7 & 14	Day 30	
Study Week	**Up to -4**	**0**	**2***	**4**	**6***	**8**	**10***	**12**	**13 & 14**	**16***	
Study Days	**Up to -28**	**1**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**91±3, 98±3**	**114±3**	
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 & 10**	**11**	
Collect Unused Study Drug/Assess drug compliance				X		X		X	X		X

Abbreviations: AE = adverse event; BP = blood pressure; CEC = Central Enrollment Committee; CGI-S/I = Clinical Global Improvement-Severity/Improvement; C-SSRS = Columbia-Suicide Severity Rating Scale; DSM-5 = Diagnostic and Statistical Manual for Mental Disorders, 5th edition; ECG = electrocardiogram; ESRS = Extra-pyramidal Symptom Rating Scale; HR = heart rate; OASES = Overall Assessment of the Speaker's Experience of Stuttering; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic(s); SSI-4 = Stuttering Severity Instrument; SSS = Subjective Screening of Stuttering; STAI-AD = State-Trait Anxiety Inventory for Adults;

[a] Informed consent must be performed prior to screening assessments.

[b] A complete physical examination will be conducted at Baseline and Week 12 and a brief physical exam as necessary per PI judgment based on reported symptoms at all other clinic visits. Vital signs will include pulse, HR, BP, orthostatic BP and pulse (done 5 minutes after being supine and then 3 minutes after standing), weight and height (height measured at Screening only).

[c] Subjects should be in a fasting state (8 hours) for laboratory tests after Visit 1 Screening. HbA1c will be measured at the Baseline and Completion/Early Termination visits.

[d] The SSI-4 will be administered by a Sponsor-approved, qualified rater. All SSI-4 interviews are conducted via video recording with the subject and interviewer in separate locations and recordings will be scored by the central rater. The central rater scores will be used for all analyses. Every attempt should be made, per subject, to perform the SSI-4 interview by the same SSI-4 interviewer at the same time and same location at each visit.

[e] The STAI form Y-1 (State) will be completed at all marked visits. The STAI form Y-2 (Trait) will be completed at Baseline visit only and administered **after** the State portion (STAI Form Y-1) as per STAI-AD Manual (page 13).

[f] A morning appointment will be made and subjects will be instructed not to take their prescribed dose of study drug within the previous 24 hours. Subjects will be instructed to record the date and time of the last administration of study drug prior to the study visit. Three PK samples will be collected at 1) pre-dose (20 to 36 hours since the last dose); and 2) post-dose between 0.5 and 1.5 hours; and 3) post-dose between 2 and 4 hours after study drug administration. Any samples should be collected at least 30 min apart. A missed PK collection due to consequences of COVID-19 or other natural disaster will not be considered a protocol deviation.

[g] Subjects will be instructed to record the date and time of the last administration of study drug prior to the study visit. A PK blood sample will be collected at the end of the visit with the time of sample collection recorded. A missed PK collection due to consequences of COVID-19 or other natural disaster will not be considered a protocol deviation.

[h] Site personnel who are delegated the responsibility to dispense study drug may coordinate the shipment of study drug to be delivered to a subject's residence in the case that restrictions, as a consequence of COVID-19 or other natural disaster, prevent in-clinic study visits.
Study drug will be dispensed for the Taper Phase reducing by 25 mg/day until off study drug.
* Weeks 2, 6, 10, and 16 are remote assessment visits. If there are any abnormal findings, the subject may be brought to the site for a full assessment. The remote assessment visit at Week 16 (30 days after the last study drug administration) is to assess any adverse events that may have occurred.
∞ PI will discuss which assessments are best suited for the Unscheduled visit with Study Medical Monitor.
[µ] Where possible safety and efficacy assessments will be made available for remote administration in the case that restrictions, as a consequence of COVID-19 or other natural disaster, prevent in-clinic study visits.

8. SELECTION AND EXCLUSION OF SUBJECTS

8.1. Subject Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subject must be able to read and write in English and provide informed consent.
2. Subjects must be ≥18 years of age at time of screening.
3. Subjects must weigh ≥ 45 kg (~ 99 lbs).
4. Subjects must satisfy DSM-5 criteria for childhood onset fluency disorder (stuttering).
5. Males and females presenting with a history of stuttering for at least 2 years with onset prior to age 8.
6. Stuttering must be developmental in nature.
7. Stuttering severity, scored by a central rater, must be of at least moderate severity on the SSI-4 at Screening and Baseline.
8. Subjects must have completed an adequate course of speech therapy as determined by the Investigator.
9. Subjects must have a qualifying IOS or Android smartphone to complete study assessments remotely, when applicable due to COVID-19 restrictions or other natural disaster.
10. Subjects must be off all medications used to treat stuttering for at least 3 months prior to Screening.
11. Females of childbearing potential who are sexually active must be using double barrier method (condom and IUD, condom and spermicide, etc.) in addition to any oral contraceptive they may be using and agree to continue use of double-barrier contraception for the duration of their participation in the study. They must also agree to use double-barrier contraception for 30 days after their last dose of study drug.

    Females are considered not to be of childbearing potential if they are either postmenopausal (amenorrhea for at least 2 years after the age of 42); or permanently sterilized (e.g., documented bilateral tubal ligation, hysterectomy, bilateral salpingo-oophorectomy, bilateral oophorectomy, etc.) for 6 months prior to Visit 1.
12. Sexually active male subjects must use a double barrier method of contraception during the study with their partner of childbearing potential and agree to continue the use of male contraception for at least 30 days after the last dose of study drug.
13. Subjects must be initially approved by a Central Enrollment Committee prior to Baseline.

8.2. Subject Exclusion Criteria

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

1. Stuttering related to a known neurological cause (e.g. head trauma, stroke, etc.).
2. Subjects who have initiated new behavioral therapies for stuttering fewer than 10 weeks prior to Baseline.
3. Subjects who have unstable medical illness or clinically significant abnormalities on laboratory tests or ECG at Screening.
4. Subjects with a significant risk of committing suicide based on history, routine psychiatric status examination, Investigator's judgment, or who had an answer of ''yes'' to either of questions 4 or 5 (currently or within the past 30 days) on the Baseline/Screening version of the Columbia Suicide Severity Rating Scale (C-SSRS).
5. Subjects who are currently pregnant or lactating.
6. Subjects who have moderate to severe renal insufficiency at Screening (eGFR < 60 mL/min/1.73m^2).
7. Subjects who have hepatic insufficiency at Screening.
8. Subjects with current or recent history DSM-5 substance use disorder (with the exception of nicotine) within 3 months from Screening.
9. Subjects with positive urine drug screen (cocaine, amphetamine, methamphetamine, tetrahydrocannabinol (THC), benzodiazepines, barbiturates, phencyclidine (PCP), or opiates at Screening or Baseline.
10. Subjects with a lifetime history of a major depressive episode.
11. Subjects with a history of attempted suicide < 1 year from Screening.
12. Subjects with a PHQ-9 score ≥10 at Screening or Baseline.
13. Subjects with a history of seizures (subjects whose only seizures were febrile seizures more than 2 years ago may be enrolled).
14. Subjects with a myocardial infarction within 6 months from Screening.
15. Subjects who have a clinically significant abnormal 12-lead ECG at Screening or Baseline (mean QT interval of >450 msec in males or >470 msec in females).
16. Subjects who have had previous treatment with ecopipam.
17. Subjects who have known allergies which exclude them from taking ecopipam tablets.
18. Subjects who have had previous treatment with an investigational study drug within 3 months of Screening.
19. Subjects receiving psychostimulants such, as amphetamines.

20. Subjects receiving anti-anxiety, anti-depressant, anti-psychotic, or anti-ADHD medications within 3 months of Screening.
21. Subjects who have a need for medications which would have unfavorable interactions with ecopipam, e.g. dopamine antagonists or agonists (including bupropion), tetrabenazine, monoamine oxidase inhibitors, or St. John's Wort.
22. Subjects who are unable to swallow tablets.
23. Any subject who in the opinion of the investigator is unsuitable for the study.

8.3. Subject Withdrawal, Removal, and Replacement Criteria

Sites must counsel subjects on safe study drug withdrawal instructions. Subjects who have taken study drug for at least three consecutive weeks beginning with the titration kit and discontinue treatment will complete Taper Phase, Week 12 procedures and be encouraged to complete all follow-up visits. These subjects will taper study drug reduced by 25 mg/day until off of drug. The date of last dose of study drug and reason(s) of premature discontinuation will be recorded in the CRF.

Subjects who discontinue/withdraw from treatment after taking less than three consecutive weeks of study drug do not need to be dispensed a taper down kit. Instead, the subject may complete an Unscheduled safety visit in lieu of completing Week 12 procedures. Please discuss which assessments are best suited for the visit with the Study Medical Monitor.

Furthermore, subjects who miss five or more consecutive doses are to be discontinued from study drug as "early termination".

The Sponsor may allow early withdrawn subjects to be replaced. The decision to replace subjects must be made after consultation with Sponsor or its representative and excludes any subjects who are withdrawn due to an AE that was treatment-related, or due to an SAE with any relatedness.

9. TREATMENT OF SUBJECTS

9.1. Concomitant Medications

For subjects who receive study treatment, any medication (including over-the-counter medications) administered to the subject during the course of the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication CRF. Non-pharmacologic 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, or the Medical History CRF for illnesses starting prior to study drug administration.

9.2. Prohibited Therapies

Prohibited therapies per the exclusion criteria include medications used to treat fluency disorder and medications which would have unfavorable interactions with ecopipam, including dopamine antagonists or agonists (including bupropion), Tetrabenazine, Monoamine oxidase inhibitors, and St. John's Wort.

Since ecopipam and its metabolite (EBS-101-40853) may inhibit CYP2D6, OATP1B1, PGP, and UGT1A9 and may induce CYP 3A and 2C enzymes, for any drug that is a substrate of these enzymes, the label for the drug should be consulted to decide whether a dose adjustment is needed. Drugs that are strong inducers of these enzymes are prohibited.

See APPENDIX I: PROHIBITED MEDICATIONS LIST.

9.3. Treatment Compliance

During the study period, subject compliance will be monitored by review of the tablet counts at the study site visits. Please see section 8.3 for guidance of when to early terminate subjects.

9.4. Randomization and Blinding

Randomization will be stratified by weight bands. Throughout the study, subjects 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 assignment. 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-based Randomization System (IWRS) and accessible by the unblinded clinical supply vendor and authorized unblinded personnel at the CRO. In the event of an emergency where knowledge of the subject's study drug assignment may affect his/her medical treatment, the Investigator may access IWRS to break the blind. Before breaking the blind, the Investigator should consult with the Sponsor or designee to ascertain the necessity of breaking the code, if possible. The IWRS will record the date and time of unblinding and Investigator will complete the reason for breaking the code. The unblinded study drug assignment information should be kept to the minimum number of site staff as possible.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Ecopipam tablets and matching placebo tablets will be provided as detailed in Table 4. Details are provided in the Emalex Study Drug Handling Manual.

Table 4: Investigational Product

	Investigational Product	
Product Name	Ecopipam	Placebo
Dosage Form	Tablets	Matching Tablets
Unit Dose of Ecopipam HCl	12.5, 50, and 75 mg	Matching unit dose tablets
Route of Administration	Oral	Oral
Physical Description	Round, biconvex, light blue film-coated tablet, plain on both sides	Round, biconvex, light blue film-coated tablet, plain on both sides
Manufacturer	Corealis Pharma Inc.	Corealis Pharma Inc.

10.2. Study Drug Packaging and Labeling

Study drug will be supplied in labeled containers by the Sponsor. Study drug is to be stored at 68ºF to 77ºF (20ºC to 25ºC) protected from light, excessive heat, open flame and combustibles, out of direct sunlight and in a well-ventilated, dry area. Ecopipam and matching placebo tablets are packaged in aluminum foil blister packs containing one tablet per blister. The aluminum blisters are secondary packaged in cardboard blister cards.

10.3. Study Drug Storage

Study drug must be stored as instructed on the study drug label. Study drug must be kept in a secure location and carefully stored at the study site within its original container and protected from light. A daily temperature log for monitoring of proper storage conditions must be maintained by the site.

10.4. Study Drug Provisions

Study drug will be provided in three 4-week blister cards for the Titration and Maintenance Phases (weeks 1-12). Each 4-week blister card is numbered by week and each week contains 8 days of study drug. Subjects will be instructed to take all of the tablets provided for numbered days 1-7. The 8th day provisions in each card should only be used to replace a lost or dropped tablet.

Study drug supplies include:

Baseline: Titration Kit (includes a 1-week Reserve Card)

Weeks 4 & 8: Maintenance Card

Week 12: Taper Kit (consists of 1 bottle for each day's dose containing single-tablet blisters, reducing by 25 mg/day until off study drug).

Subjects will be dispensed a 4-week blister card at each study visit through Week 8. The Reserve card consists of 1 week of maintenance dose study drug for continued dosing if a study visit needs to be rescheduled outside of the visit window. Sites must counsel subjects when it is appropriate for them to dose with the Reserve card. At the Week 12 study visit, a Taper Kit will be dispensed.

Site personnel who are delegated the responsibility to dispense study drug may coordinate the shipment of study drug to be delivered to a subject's residence in the case that restrictions, as a consequence of COVID-19 or other natural disaster, prevent in-clinic study visits.

10.5. Study Drug Regimen

Ecopipam HCl at a target dose of ~2 mg/kg/day or matching placebo will be administered during the 4-week titration phase and the 8-week maintenance phase for each of the weight bands:

Weight (kg)	TREATMENT PERIOD				
	Titration Phase (Weeks 1-4)				Maintenance Phase (Weeks 5-12)
	Dose (mg) Week #1	Dose (mg) Week #2	Dose (mg) Week #3	Dose (mg) Week #4	Dose (mg) Week #5-12
45 to ≤68	25 (2 × 12.5)	50	75	100 (2 x 50)	100 (2 x 50)
69 to ≤83	25 (2 × 12.5)	50	100 (2 x 50)	150 (2 × 75)	150 (2 × 75)
>83	25 (2 × 12.5)	50	100 (2 x 50)	200 (4 x 50)	200 (4 x 50)

All doses will be administered PO once daily in the evening before bedtime. Subjects who have changes in weight during the study will not have their doses adjusted for the duration of the study.

At the end of the Treatment Period or Early Discontinuation, subjects will taper study drug reduced by 25 mg/day until off of drug.

10.6. Dose Rationale

An ecopipam HCl target dose of ~2 mg/kg/day with titration is targeted in adult subjects using the dosage regimen detailed in Section 10.5.

This dosing regimen was chosen based on results from 2 clinical trials and modeling and simulation of dosing ecopipam on a mg/kg basis with the results and important information summarized below:

- Results from the University of California Riverside Clinical Summary: Phase 2a Clinical Study in Adults with Childhood Onset Fluency Disorder demonstrating proof of concept activity and well tolerated dose of 100 mg/day in adult subjects treated for 8 weeks.
- A double-blind, placebo-controlled, crossover study of 40 subjects with Tourette syndrome aged 7 to 17 years receiving ecopipam HCl at 50 mg (if <75 pounds) or 100 mg (if >75 pounds), after a titration, showed that it is likely that ecopipam has modest efficacy based on a post-hoc analysis (Study PSY302, the most recent clinical study with ecopipam);
- 2 mg/kg targets a mg/kg dose that is above the median mg/kg dose in 75% of subjects in Study PSY302, with the remaining 25% of subjects having a mg/kg dose that is substantially below the 95th percentile from Study PSY302;
- The predicted plasma concentration-time curves for the median, 5th percentile and 95th percentile are within the exposures studied in PSY302 and similar to other proposed dosing regimens;
- The animal:human ratios for the active moieties (unconjugated parent plus active metabolite, EBS-101-40853) are adequate based on the NOAEL in the 3-month GLP

toxicology study for mice (30 mg/kg), the 3-month GLP toxicology study in rhesus monkeys at 12 mg/kg, and the 1-year GLP toxicology study in cynomolgus monkeys at 12 mg/kg and do not differ from those already exposed in Study PSY302. For rhesus and cynomolgus monkeys, the main toxicities observed at 12 mg/kg were decreased activity, decreased appetite, and decreased defecation. For cynomolgus monkeys, these AEs were reported during the first 1 to 3 weeks (hence, the need for titration in clinical trial EBS-101-COFD-201);

- In Study PSY302, the treatment emergent adverse events (TEAEs) were gastrointestinal disorders (e.g., nausea, upper abdominal pain), general disorders and administrative site conditions (e.g., decreased appetite, fatigue), and nervous systems disorders (e.g., somnolence, headache, sedation). The current study will incorporate a four-week titration which has the potential to improve tolerability;
- Doses higher than ~2 mg/kg may not be well tolerated and doses higher than ~2 mg/kg would result in animal:human exposures significantly lower than 1. See Table 5; and
- As this is the first double-blind, placebo-controlled study of ecopipam in COFD, studying a single dose will provide an equal chance for a subject to receive drug or placebo (potentially increasing ability to detect an efficacy signal) with the smallest number of subjects being exposed to drug. The 1:1 randomization will allow for decreased bias and facilitate the determination of the drug's effect for future clinical investigations.

Table 5: Animal:Human Exposure Ratios for Highest Proposed Dosage Regimen of Ecopipam HCl

Dose Group	PK	Mice: Human Ratio[b]	Rhesus Monkey: Human Ratio		Cynomolgus Monkey: Human Ratio	
		30 mg/kg	3 mg/kg	12 mg/kg	3 mg/kg	12 mg/kg
Combined AUC[a] (ng*hr/mL)						
Full Dose ~2 mg/kg	583	4.30x	0.52x	1.48x	0.53x	2.65x
Combined C_{max}[a] (ng/mL)						
Full Dose ~2 mg/kg	67.4	4.30x[c]	0.36x	0.85x	0.39x	2.21x

[a] Animal: human ratios were calculated based on combined unconjugated parent ecopipam plus active metabolite EBS-101-40853 AUC and C_{max}.
[b] The ratios for rats at 6 mg/kg are not included due to the fact that the assay sensitivity was not adequate (LLOQ=0.5 μg/mL), the AUC was determined with ≤3 data points, and there were too few concentrations above the LLOQ to determine the C_{max}

10.7. Study Drug Accountability

Site personnel delegated with the responsibility to manage/handle study drug will enter receipt, dispensing, and return of all study drug using IWRS. Final study drug accountability will be conducted at each site's study close out visit and the Investigator must explain any discrepancy.

On close-out of the site, all used cards and bottles and unused investigational product must be shipped to the Emalex-designated location. Returned and unused study drug will be monitored against the IWRS Drug Dispensing Report.

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 who has been delegated with the activity, 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

11.1. Primary Efficacy Assessment

The primary efficacy endpoint for this trial is the change in SSI-4 from Baseline to end of therapy at Week 12 for subjects receiving ecopipam compared with subjects receiving placebo as measured by a central rater.

11.1.1. Stuttering Severity Instrument – Fourth Edition (SSI-4)

The SSI-4 is a reliable and valid norm-referenced stuttering assessment that can be used for both clinical and search purposes. It takes 15-20 minutes to complete. It measures stuttering severity in both children and adults in the four areas of speech behavior:

1. frequency
2. duration
3. physical concomitants
4. naturalness of the individual's speech.

Frequency is expressed in percent syllables stuttered and converted to scale scores of 2-18. Duration is timed to the nearest one tenth of a second and converted to scale scores of 2-18. The four types of Physical Concomitants are converted to scale scores of 0-20. The SSI-4 can also be used in conjunction with the Stuttering Prediction Instruments for Young Children (SPI).

SSI-4 was normed on a sample of 72 preschool-aged children, 139 school-aged children, and 60 adults. It has four components, each of which is used to assess and monitor the stuttering severity in both children and adults for clinical and research use: (1) Examiner's Manual and Picture Plates, (2) Test Record and Frequency Computation Forms, (3) Subjective Stuttering Scales, and (4) Computerized Scoring of Stuttering Severity (Software Version 2.0).

The primary endpoint will be assessed with a Mixed Model for Repeated Measures (MMRM) which will include fixed effects for treatment, visit (categorical week in trial), interaction between treatment and visit, center and a covariate for baseline score. Taking consideration of missing data, multiple imputation or tipping point method may be used as a sensitivity analysis and will be detailed in the statistical analysis plan.

11.1.1.1. Stuttering Severity Instrument – Fourth Edition (SSI-4) Interview and Scoring

The SSI-4 will be administered by a dedicated site interviewer who is trained and certified by the Sponsor-approved rater training vendor. The dedicated SSI-4 site interviewer will not conduct any other study assessments nor interact further with the subject. This is intended to reduce the potential familiarity a subject may feel toward the administrator of the primary efficacy instrument.

Centralized SSI-4 scoring is intended to reduce variability in scale scoring and increase standardized administration techniques through careful examination of all study visits. External, unbiased scoring of the SSI-4 will help to minimize the enrollment of ineligible subjects and improve the quality of the data while reducing variability in scoring. (Davidow & Scott, 2017).

All SSI-4 interviews are conducted via video streaming and recorded with the subject and interviewer in separate locations using a device provided by the qualified vendor. Every attempt should be made, per subject, to perform the SSI-4 interview by the same SSI-4 interviewer, at the same time and same location at each visit.

The recorded SSI-4 interviews will be scored by the central raters who are calibrated, expert clinicians.

Investigators will be informed of the central rater's scored assessment of stuttering severity at the Screening and Baseline visits for eligibility purposes. Thereafter, the SSI-4 scores from all relevant visits will be transferred to the EDC system. The central rater scores will be used for all analyses.

11.2. Secondary Efficacy Assessments

Key Secondary Endpoints:

- Change in the SSS score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12
- Change in the CGI-S score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12

Other Secondary efficacy endpoints include:

- Change in the OASES score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12
- Change in the CGI-I score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12
- Change in the SSI-4 percentage of syllables stuttered for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to the end of therapy at Week 12
- Change in the SSI-4 frequency sub-score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to the end of therapy at Week 12
- Change in the SSI-4 duration sub-score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to the end of therapy at Week 12
- Change in OASES Section IV score for subjects receiving ecopipam compared with subjects receiving placebo from Baseline to end of therapy at Week 12
- Changes in all primary and secondary endpoints for subjects receiving ecopipam at Weeks 4 and 8

Rank order of hierarchy of the primary, key secondary, and other secondary endpoints will be outlined in the Statistical Analysis Plan.

11.2.1. Clinical Global Impression

The CGI consists of two reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms (Guy, 1976). The improvement scale (CGI-I) ranges from 1 =

"very much improved" to 7 = very much worse." The severity scale (CGI-S) ranges from 1 = "not ill at all" to 7 = "among the most extremely ill."

11.2.2. Subjective Screening of Stuttering (SSS)

The SSS research edition is designed to quantify the selected self-reports of people who stutter prior to, during, and following their treatment (Riley et al, 2004). The three areas screened by the SSS are perceived stuttering severity, the level of internal or external locus of control, and reported word or situation avoidance. Each of the areas has two or three items rated for three audiences on a 1 to 9, equal appearing scale in which 1 represents "normal" or target level and 9 is the most severe.

The lookback period of the form is one week.

11.2.3. Overall Assessment of the Speaker's Experience of Stuttering (OASES-A) Adult

The OASES is a measure of the effect of stuttering on a person's life (OASES-A; Yaruss & Quesal, 2006, 2010). The OASES is designed to provide a comprehensive assessment of the stuttering disorder from the speaker's perspective. It gives clinicians meaningful insights into the person who stutters experiences that can be used in the diagnostic process, for treatment planning, and in outcomes assessment.

Each question is scored on a 5 point Likert scale. Responses are totaled into Impact Scores and Impact Ratings (mild through severe). Scoring can be completed for the entire test, as well as for each of the four sections individually. These sections examine:

- General Information
- Reactions to Stuttering
- Communication in Daily Situations
- Quality of Life

11.3. Pharmacokinetic Assessments

Blood samples will be collected to measure concentrations of ecopipam and/or its major (active) metabolite at Weeks 4 and 12. Blood samples will be processed as outlined in the laboratory manual and serum/plasma will be frozen, shipped and analyzed.

Subjects will be instructed to withhold their at-home administration of study drug the evening prior to the Week 4 visit and record the last date and time of study drug administration. The Week 4 visit will be scheduled for a morning appointment. An intravenous catheter will be placed, and the subject will have three samples collected at the following time windows:

1. predose (20 to 36 hours since the last dose)
2. between 0.5 and 1.5 hours after administration of study drug, and
3. between 2 and 4 hours after study drug administration.

Any samples should be collected at least 30 min apart.

On the Week 12 visit, the time of study drug administration should be recorded for the last dose of study drug (the last dose is expected to have been administered the evening prior to the visit). A blood sample will be collected at the end of the visit with the time of sample collection recorded.

A missed collection of a PK sample due to consequences of COVID-19 or other natural disaster will not be considered a protocol deviation.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety will be assessed by monitoring and recording all Adverse Events (AEs) and Serious Adverse Events (SAEs) at all study visits. Regular monitoring of hematology, blood chemistry, HbA1c, urine values, vital signs, physical examinations, and ECGs as detailed in Table 3. Subjects will have AE and other safety parameters assessed by phone or video conference at Weeks 2, 6 and 10 and 30 days after the last study drug administration. Signs or symptoms of withdrawal, abuse, and dependence will be monitored throughout the study.

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

The C-SSRS is a low burden (approximately 5 minutes for completion) instrument to assess both suicidal behavior and ideation (Posner et al, 2011). 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.

12.1.1.1. Public Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a validated, 9-question tool to assess for the degree of depression present in an individual (Kroenke et al, 2001). The PHQ-9 incorporates DSM-4 depression diagnostic criteria with other leading major depressive symptoms into a brief, self-report tool. The tool 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 Investigator will perform suicide risk assessment in subjects who respond positively to Question 9.

A follow up, non-scored question on the PHQ-9 screens and assigns weight to the degree to which depressive problems have affected the subject's level of function.

The lookback period of the form is two weeks. Completion time is under 5 minutes.

12.1.1.2. State-Trait Anxiety Index-Adult (STAI-AD)

The STAI-AD is a commonly used self-report to measure two types of anxiety: state anxiety (or anxiety about an event), and trait anxiety (or anxiety level as a personal characteristic). (Spielberger et al, 1983). The STAI has 40 items, 20 items allocated to each of the S-Anxiety and T-Anxiety subscales.

The STAI-AD is a psychological inventory based on a 4-point Likert scale. Responses for the S-Anxiety scale assess intensity of current feelings "at this moment": 1) not at all, 2) somewhat, 3) moderately so, and 4) very much so. Responses for the T-Anxiety scale assess frequency of feelings "in general": 1) almost never, 2) sometimes, 3) often, and 4) almost always. Higher scores are positively correlated with higher levels of anxiety.

The intent of the T-Anxiety scale is to characterize a long-standing trait and as such, the T-Anxiety is less responsive to change as compared to the S-Anxiety. Because of this, the T-Anxiety will only be completed at the Baseline visit where the S-Anxiety will be completed at Baseline and each subsequent in-clinic study visit.

The STAI-AD is appropriate for those who have at least a sixth-grade reading level. Completion time is approximately 10-15 minutes.

12.1.1.3. Extra-pyramidal Symptom Rating Scale (ESRS)

The ESRS is a clinician-reported instrument developed to assess four types of drug-induced movement disorders (DIMD): Parkinsonism, akathisia, dystonia, and tardive dyskinesia (TD) (Chouinard & Margolese, 2005). The ESRS consists of:

A) four subscales:

- a questionnaire of EPS or DIMD
- an examination of Parkinsonism and akathisia
- an examination of dystonia
- an examination of dyskinesia

and B) four CGI-S scales assessing:

- TD
- Parkinsonism
- Dystonia
- akathisia

The lookback period of the form is 7 days. Administration time is approximately 10-15 minutes.

12.1.1.4. Vital Signs

Vital signs will be collected at each study visit per Table 3. They include blood pressure, orthostatic blood pressure and pulse (after being supine for 5 minutes and 3 minutes after standing) pulse, height and weight. Height will be measured at the Screening visit only.

12.1.1.5. Electrocardiogram (ECG)

Sites will assess subjects with a 12-lead ECG at clinic visits per Table 3. Investigators will instruct subjects to follow-up with care as appropriate upon evidence of new or worsening abnormal ECG readings.

12.1.1.6. Central Laboratory Tests

Subjects should be in fasting state (8 hours) for all blood laboratory tests collected at study visits after Visit 1 screening (see Table 3). Study sites will follow the laboratory manual collection, handling, storage, and shipping instructions for the tests below.

Hematology	Red blood cell count, hemoglobin, hematocrit, platelets, and white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils). Lymphocyte bands will be tested upon manual differential for abnormal results.
Chemistry	Glucose, calcium, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, globulin
Electrolytes	Sodium, potassium, chloride, bicarbonate

Liver function tests	Alkaline phosphatase (ALP), aspartate amino transferase (AST), alanine amino transferase (ALT), total bilirubin, direct bilirubin
Renal function parameters	Blood urea/blood urea nitrogen (BUN), creatinine. Note: eGFR calculation (Cockcroft Gault Calculation) during Screening only
Special Parameters	Hemoglobin A1c (HbA1c) (at Baseline and Week 12 only)
Urine	Complete urinalysis includes color, appearance, specific gravity, pH, protein, glucose, ketones, and blood with microscopic examination for positive protein or blood results

12.1.1.7. Local Laboratory Tests

Urine will be collected at select clinic visits. See Table 3. Study sites will follow the laboratory manual collection, handling, and result recording instructions for the tests below.

Urine Pregnancy Test	Females of childbearing potential only. A positive urine pregnancy test will require a qualitative, serum hCG test.
Urine Drug Screen	cocaine, amphetamine, methamphetamine, tetrahydrocannabinol (THC), benzodiazepines, barbiturates, phencyclidine (PCP), opiates

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

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 disease temporally associated with the use of a study drug, whether or not related to the study drug.

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 drug
- 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 stuttering 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 or not they are related to the study, must be recorded on forms provided by Sponsor or its representatives.

Signs or symptoms of withdrawal, abuse, and dependence will be monitored throughout the study and recorded as an AE.

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 fulfils 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 has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by the Sponsor or its representatives.

12.2.1.3. Adverse Events of Special Interest

Adverse events of special interest (AESI) include weight gain, extrapyramidal symptoms, convulsions, depression and suicide/self-injury, drug abuse, drug dependence, drug withdrawal, dyslipidemia, hepatic disorders, hyperglycemia/new onset diabetes mellitus, neuroleptic malignant syndrome, parkinsonism, and psychosis/psychotic disorders.

12.2.1.4. 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 evaluation of safety data for the Clinical Study Report. Significant adverse events of particular 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.

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 by 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 or not 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.

12.5. Recording and Reporting Pregnancy

Should a pregnancy of a subject or partner occur, it must be reported and recorded on Sponsor-approved pregnancy form. Pregnancy in itself 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 to Premier Pharmacovigilance within 24 hours of the first awareness of the event:

Email Address: GlobalPV-US@premier-research.com
Fax no.: (215) 972-8765

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.

12.6. Recording and 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 SAEs 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 within 24 hours of the first awareness of the event:

Email Address: GlobalPV-US@premier-research.com
Fax no.: (215) 972-8765

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 be sent to the Sponsor's representatives within 24 hours of receipt and completed on a follow-up SAE form.

The Sponsor is 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 trial. Each Principal Investigator is responsible for notifying his or her IRB or IEC of these additional SAEs.

13. STATISTICS

This section presents a summary of the planned statistical analyses. A Statistical Analysis Plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock. All data analyses will be performed by the Sponsor or its representatives after the study is completed and the database is locked. 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 collected via remote administration when visits are restricted due to consequences of COVID-19 or other natural disaster. These will be specified in the SAP.

Continuous, quantitative, variable summaries will include the number of subjects (N) with non-missing values, mean, standard deviation, median, minimum, and maximum.

Categorical or qualitative variable summaries will include the frequency and percentage of subjects who are in the particular category. The denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment group, unless otherwise specified.

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 and have at least one post-baseline efficacy evaluation completed. The mITT population will be used for the analysis of primary and secondary efficacy endpoints. Subjects will be analyzed by randomized treatment.

The Per-Protocol (PP) population will include subjects from mITT population who have no major protocol deviations. 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. Subjects will be analyzed by randomized treatment.

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. Subjects will be analyzed by actual treatment received.

The PK population will include all subjects from safety population who have a valid concentration measurement.

13.2. Planned Analysis

13.2.1. Efficacy Analysis

The primary efficacy endpoint for this trial will be the change in SSI-4 from Baseline to end of therapy at Week 12 for subjects receiving ecopipam compared to subjects receiving placebo. The analysis of primary efficacy endpoint will be evaluated for the mITT and PP populations according to the randomized treatment.

The primary endpoint will be assessed with a Mixed Model for Repeated Measures (MMRM) using (SAS MIXED procedure with REPEATED statement) with no imputation. The model will include fixed effects for treatment, visit interaction between treatment and visit, center, and covariate for baseline score. Taking consideration of missing data, multiple imputation or tipping point method may be used as a sensitivity analysis.

Secondary endpoints will be analyzed using MMRM if appropriate. The treatment difference at Week 4, 8 and 12 can be estimated based on MMRM. All secondary endpoints will be analyzed in the mITT population according to randomized treatment.

All efficacy endpoints may also be summarized by treatment group. The fixed-sequence statistical strategy will be used to test all efficacy endpoints in a predefined order.

The full details of the analyses, including sensitivity analyses, will be provided in the SAP.

13.2.2. Safety Analysis

All safety data will be summarized in Safety population according to the actual treatment received. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1 or higher.

Treatment-emergent adverse events (TEAEs) are defined as adverse events that are newly occurring or worsening after the first dose of study drug. The incidence of TEAEs will be summarized by treatment group, by system organ class (SOC) and preferred term (PT), by severity and by relationship to study drug. Serious TEAEs and TEAEs leading to the study termination will also be summarized by SOC, PT, and treatment group.

Descriptive statistics for observed values and change from baseline in laboratory data, vital sign, physical examination and ECG will be summarized by treatment group and visit.

The C-SSRS, ESRS, STAI-AD, and the PHQ-9 will also be summarized descriptively.

13.2.3. Pharmacokinetics Analysis

The pharmacokinetics concentrations of ecopipam and its major metabolites at weeks 4 and 12 will be summarized descriptively in Pharmacokinetics population. The data may be combined with data from other studies of ecopipam and population pharmacokinetic analysis may be conducted. If conducted, this analysis will be described in a separate analysis plan and report.

13.2.4. Pharmacokinetic/Pharmacodynamic Analysis

The relationship between plasma exposure measurements (e.g., maximum plasma concentration, trough concentration, or area under the curve of ecopipam and/or EBS-101-40853) and therapeutic response or safety may be investigated. If conducted, this analysis will be described in a separate report.

13.3. Sample Size Justification

A sample size of approximately 68 subjects (34 subjects per treatment arm) will provide ≥80% power to detect a 20% difference between ecopipam and placebo groups on change from Baseline to Week 12 for the SSI-4, with standard deviation = 24.7 and alpha = 0.05, assuming 10% drop out.

14. 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 with regard to 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 forms, 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 recorded.
- 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)

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 (LSO) 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. See Section 14.2.

The Sponsor or its designee will implement and maintain quality assurance and quality control systems with written SOPs to ensure that trials 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 and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

16.3. Written Informed Consent

The Principal Investigator(s) at each 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 they 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.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

16.4. Subject Confidentiality

The information obtained during the conduct of this clinical trial 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 trial for the development of ecopipam. The trial Investigator is obliged to provide the Sponsor with complete test results and all data developed in this trial, as described in this protocol.

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 trial 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 trial or in publications, the subjects' identity will remain confidential.

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. LIST OF REFERENCES

Alm P. Stuttering and the basal ganglia circuits: a critical review of possible relations. Journal of Communication Disorders. 2004;37:325-69.

Chang SE, Angstadt M, Chow HM, Etchell AC, Garnett EO, Choo AL, et al. Anomalous network architecture of the resting brain in children who stutter. J Fluency Disord. 2018;55:46-67.

Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophr Res. 2005;76(2-3):247-65. Epub 2005 Apr 18.

Davidow JH, Scott KA. Intrajudge and Interjudge Reliability of the Stuttering Severity Instrument-Fourth Edition. Am J Speech Lang Pathol. 2017;26(4):1105-19. doi: 10.1044/2017_AJSLP-16-0079.

Gilbert DL, Murphy TK, Jankovic J, Budman CL, Black KJ, Kurlan RM, et al. Ecopipam, a D1 receptor antagonist, for treatment of tourette syndrome in children: A randomized, placebo-controlled crossover study. Mov Disord. 2018;33(8):1272-80.

Guy W. The Clinical Global Impression Scale. In ECDEU Assessment Manual for Psychopharmacology-Revised. Rockville, MD, U.S. Department of Health, Education, and Welfare, ADAMHA, NIMH, Psychopharmacology Research Branch, 1976, pp 218-222

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13.

Maguire GA, Riley GD, Franklin DL, Gottschalk, LA. Risperidone for the treatment of stuttering. Journal of Clinical Psychopharmacology. 2000;20(4);479-82.

Maguire GA, Yu BP, Franklin DL, Riley GD. Alleviating stuttering with pharmacological interventions. Expert Opin Pharmacother. 2004;5(7):1565-71.

Maguire GA, Riley GD, Franklin DL, Maguire ME, Nguyen CT, Brojeni PH. Olanzapine in the treatment of developmental stuttering: a double-blind, placebo-controlled trial. Annals of Clinical Psychiatry. 2004b;16:63-7.

Maguire GA, et al. Ecopipam as a pharmacologic treatment of stuttering. Ann Clin Psychiatry. 2019.

Maguire GA, Riley GD, Yu BP. A neurological basis of stuttering? Lancet Neurol. 2002;1(7):407.

Maguire G, Yeh C, Ito B. Overview of the diagnosis and treatment of stuttering. Journal of Experimental and Clinical Medicine. 2012;4(2):92-7.

Nelson, Maguire, LaSalle, Lochhead, Castanos. Ecopipam as a pharmacological treatment of stuttering. Submitted to Annals of Psy 2018.

Posner K, Brown GK, Stanley B, B rent DA, Yeshiva KV, Oquendo MA, et al. The Columbia-suicide severity rating scale: Initial validity and internal consistency findings from three multi site studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

Riley GD. Stuttering severity instrument for children and adults (SSI-4) 4th ed. Pro-Ed, Inc; Austin, TX: 2009.

Riley J, Riley G, Maguire G. Subjective screening of stuttering severity, locus of control and avoidance. J Fluency Disord. 2004; 29: 51-62.

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Wu JC, Maguire G, Riley G, Lee A, Keator D, Tang C, et al. Increased dopamine activity associated with stuttering. Neuroreport. 1997;8:767-70.

Yaruss JS, Quesal RW. *Overall Assessment of the Speaker's Experience of Stuttering.* Bloomington, MN: Pearson Assessments; 2010.

Yaruss JS, Quesal RW. Overall Assessment of the Speaker's Experience of Stuttering (OASES): Documenting multiple outcomes in stuttering treatment. J Fluency Disord. 2006;31(2):90-115.

APPENDIX I: PROHIBITED MEDICATIONS LIST

Examples of prohibited medications in this appendix are provided below. This is not a complete list. Please contact the medical monitor if you have questions about prohibited medications.

- Other medications used to treat fluency disorder are prohibited.
- Dopamine depleting medications are prohibited.
- D2 receptor antagonists are prohibited.

Prohibited anti-Psychotic, anti-Anxiety, anti-Depressant and anti-ADHD Medications	
Alprazolam	Haloperidol
Aripiprazole	Loxapine
Atomoxetine	Methylphenidate
Chlorpromazine	Paliperidone
Cisapride	Paroxetine
Citalopram	Perphenazine
Clomipramine	Pimozide
Clonidine	Propranolol
Desipramine	Quetiapine
Dextroamphetamine	Risperidone
Doxepin	Thioridazine
Dronedarone	Topiramate
Droperidol	Trimipramine
Fluoxetine	Venlafaxine
Guanfacine	Ziprasidone

Prohibited Medications for the Treatment of Tics	Other Prohibited Medications
Baclofen	Chloroethylnorapomorphine
Clonazepam	Cinnarizine
Duetetrabenazine	Desmethoxyfallypride
Guanfacine	Domperidone
Reserpine	Eticlopride
Tetrabenazine	Fallypride
Valbenazine	Hydroxyzine
	Itopride
	Metclopropramide

Strong Inducers of Drug Metabolism	
Apalutamide	Mitotane
Avasimibe	Phenobarbital
Carbamazepine	Phenytoin
Enzalutamide	Rifampin
Ivosidenib	Rifapentine
Lumacaftor	St John's Wort extract

Sensitive CYP2D6 substrates: dose of these sensitive CYP2D6 substrates may need to be reduced based on their label	
Codeine	Perhexiline
Dextromethorphan	Prajmaline
Deutetrabenazine	Propafenone
Eliglustat	Repinotan (IV)
Encainide	Tamoxifen
Enclomiphene	Tolperisone
Ibogaine	Tolterodine
Metoprolol	Tramadol
Methoxyphenamine	Traxoprodil
Nebivolol	Tropisetron
Nicergoline	Vernakalant

OATP1B1 substrates: dose of these OATP1B1 substrates should be adjusted based on their label	
Bosentan	Glecaprevir
Cerivastatin (acid)	Letermovir
Clazosentan	Pitavastatin (acid)
Danoprevir	Rosuvastatin (acid)
Eluxadoline	Velpatasvir
Fimasartan	Voxilaprevir
Fluvastatin	

UGT1A9 substrates: dose of these UGT1A9 substrates should be adjusted based on their respective labels
Clopidogrel
Furosemide
Mycophenolic acid
Probenecid
Propofol

PGP substrates: dose of these PGP substrates should be adjusted based on their respective labels			
Acalabrutinib	Deflazacort	Letermovir	Rivaroxaban
Adafosbuvir (AL-335)	Dicloxacillin	Linezolid	Rosuvastatin (acid)
Albendazole	Digoxin	Loperamide	Saquinavir
Aliskiren	Docetaxel	Losartan	Selexipag
Alisporivir	Domperidone	Maraviroc	Simeprevir
Ambrisentan	Doravirine	Mirabegron	Simvastatin (lactone)
Amd070	Doxorubicin	Mitoxantrone	Sirolimus
Amenamevir	Edoxaban	Morphine	Sofosbuvir
Apixaban	Elbasvir	Nadolol	Sotrastaurin
Asunaprevir	Emtricitabine	Naldemedine	Tacrolimus
Atecegatran metoxil	Erlotinib	Naloxegol	Talinolol
Atorvastatin (acid)	Erythromycin	Nevirapine	Tedisamil
Avatrombopag	Etoposide	Nintedanib	Teneligliptin
Azithromycin	Everolimus	Octreotide	Tenofovir
Betrixaban	Fentanyl	Olodaterol	Ticagrelor
Bictegravir	Fexofenadine	Paclitaxel	Velpatasvir
Buprenorphine	Glecaprevir	Paritaprevir	Venetoclax
Celiprolol	Idarubicin	Pazopanib	Verapamil
Cerivastatin (acid)	Indinavir	Phenytoin	Vinblastine
Colchicine	Irinotecan	Pibrentasvir	Vincristine
Copanlisib	Itraconazole	Pravastatin (acid)	Voclosporin
Cp-481,715	Ivosidenib	Proguanil	Ximelagatran
Cyclosporine	Lapatinib	Quinidine	
Dabigatran	Larotrectinib	Ranitidine	
Danoprevir	Ledipasvir	Ranolazine	