ECOPIPAM (EBS-101)
EBS-101-CL-001

IND Number:	109746
EudraCT Number:	2019-000281-37
Protocol Title:	A Multicenter, Placebo-Controlled, Double-Blind, Randomized, Parallel-Group, Phase 2b Study to Evaluate the Efficacy and Safety of Ecopipam Tablets in Children and Adolescent Subjects with Tourette's Syndrome
Indication Studied:	Children and Adolescent Subjects with Tourette's Syndrome
Protocol Version/Date:	6.0, Amendment 5, 13 April 2020
Sponsor Address:	Emalex Biosciences, Inc. 300 North Wabash Avenue, Suite 3500 Chicago, IL, 60611

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

1. PROTOCOL AMENDMENT CHANGES

In addition to the changes summarized in this section, minor editorial and formatting changes were made to enhance clarity and readability.

Section: Title Page

Existing Text

1033 Skokie Boulevard, Suite 600

Northbrook, IL 60062

Revised Text

300 North Wabash Avenue, Suite 3500

Chicago, IL, 60611

Rationale for Amendment

Updated to reflect new location of Emalex Biosciences, Inc.

Section: Investigator's Agreement

Existing Text

EBS-101-CL-101

Revised Text

EBS-101-CL-001

Rationale for Amendment

Correction of typographical error

Section: Table 1: Emergency Contact Information

Existing Text

Role in Study	Name	Contact Information
Clinical Study Leader	PPD	PPD PPD

Revised Text

Role in Study	Name	Contact Information
Clinical Study Leader	PPD	PPD PPD

Rationale for Amendment

Updating telephone information at new location for Emalex Biosciences personnel.

Section: Synopsis/Studied period (years)

Existing Text

Estimated date last subject completed: Q2 2020

Revised Text

Estimated date last subject completed: Q2 2022

Rationale for Amendment

Timeline extended according to delays incurred during the COVID-19 pandemic.

Sections: Synopsis/Methodology and 7.1 Study Design

Existing Text

After the screening period, subjects will return to the clinic at Baseline and 4, 6, 8 and 12 weeks after Randomization. Subjects will have telephone visits on Weeks 2 and 10 to assess adverse events and other safety parameters. Efficacy assessments will be conducted at weeks 4, 6, 8 and 12. Safety assessments will be conducted at these visits as well. A Follow Up visit will be conducted in the clinic 7 and 14 days after the last dose of study medication. Subjects will also be contacted 30 days after the last dose of study medication to determine any adverse events. At study completion or early termination, subjects will be tapered off study drug as outlined in the protocol.

Revised Text

After the screening period, subjects will return to the clinic at Baseline and 4, 6, 8 and 12 weeks after Randomization. Study Visits at Weeks 4, 6, 8 and 12 after randomization may be completed in locations other than clinic and/or safety and efficacy assessments required at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event. Subjects will have telephone visits on Weeks 2 and 10 to assess adverse events and other safety parameters. Efficacy assessments will be conducted at Weeks 4, 6, 8 and 12. Safety assessments will be conducted at these visits as well. A Follow Up visit will be conducted in the clinic 7 and 14 days after the last dose of study medication. The follow up visits on Day 7 and 14 after the last dose of study medication may be completed in locations other than clinic and/or safety and efficacy assessments required at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event. Subjects will also be contacted 30 days after the last dose of study medication to determine any adverse events. At study completion or early termination, subjects will be tapered off study drug as outlined in the protocol.

Rationale for Amendment

Alternate remote monitoring procedures implemented for safety purposes in response to the COVID-19 pandemic.

Sections: Synopsis/Inclusion Criteria and 8.1 Inclusion Criteria

Existing Text

11) The subject has received an adequate trial of non-pharmacological therapy without adequate response prior to study enrollment as documented by the Investigator.

Revised Text

11) For subjects enrolled outside of the United States and Canada, the subject has received an adequate trial of non-pharmacological therapy without adequate response prior to study enrollment as documented by the Investigator.

Rationale for Amendment

The variability of access to formalized psychological treatment for TS in the US and Canada for patients in different regions creates an irregularity. However, the severity of illness will continue to be assessed by the YGTSS.

Section: Synopsis/Exclusion Criteria

Existing Text

19) Subjects receiving anti-depressant, anti-anxiety or anti-ADHD medications unless the dosage has been stable for a minimum of 2 weeks prior to Screening and not prescribed to relieve the neurological symptoms related to TS.

Revised Text

19) Subjects receiving anti-depressant, anti-anxiety or anti-ADHD medications unless the dosage has been stable for a minimum of 4 weeks prior to Screening and not prescribed to relieve the neurological symptoms related to TS.

Rationale for Amendment

Correction made to the inclusion criteria in the synopsis to match the corresponding item in Section 8.1 Inclusion Criteria.

Sections: Synopsis/Exclusion Criteria and 8.2 Exclusion Criteria

Existing Text

22) Subjects who have initiated new behavioral therapies to treat TS fewer than 10 weeks prior to Baseline visit.

Revised Text

22) Subjects who have initiated new behavioral therapies fewer than 10 weeks prior to Baseline visit.

Rationale for Amendment

The impact of behavioral treatment for any indication may lead to improvement of TS symptoms.

Sections: Synopsis/Exclusion Criteria and 8.2 Exclusion Criteria

Existing Text

14) Subjects with a history of seizures (excluding febrile seizures that occurred >2 years prior to Screening).

Revised Text

14) Subjects with a history of seizures (excluding febrile seizures that occurred <2 years prior to Screening).

Rationale for Amendment

Significant typographical error corrected.

Sections: Synopsis/Exclusion Criteria and 8.2 Exclusion Criteria

Existing Text

None

Revised Text

25) Any subject who in the opinion of the investigator is not a suitable candidate for the study.

Rationale for Amendment

In addition to formalized exclusion criteria this criterion is to provide investigators the ability to ensure that subjects who may not be suitable for the study can be excluded.

Section: Synopsis/Safety

Existing Text

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 the baseline and completion/early termination visits. Regular measurement of vital signs and the performance of a physical examination and an ECG will occur at Screening, Baseline and Weeks 4, 6, 8 and 12 and 7 and 14 day Follow Up visits. An additional assessment will include the Columbia-Suicide Severity Rating Scale (C-SSRS) (all Visits except 30 day Follow up visit). Additional safety outcomes (Baseline and Weeks 4, 6, 8 and 12) will include

the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Swanson, Nolan and Pelham (SNAP-IV) questionnaire, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), the Children's Depression Rating Scale-Revised (CDRS-R), the Giles de la Tourette Syndrome – Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) and the Pediatric Anxiety Rating Scale (PARS).

Revised Text

Study Visits at Weeks 4, 6, 8 and 12 after randomization may be completed in locations other than clinic and/or safety assessments required at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event. Safety will be 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 the baseline and completion/early termination visits. Regular measurement of vital signs and the performance of a physical examination and an ECG will occur at Screening, Baseline and Weeks 4, 6, 8 and 12 and 7 and 14 day Follow Up visits. An additional assessment will include the Columbia-Suicide Severity Rating Scale (C-SSRS) (all Visits except 30 day Follow up visit). Additional safety outcomes (Baseline and Weeks 4, 6, 8 and 12) will include the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Swanson, Nolan and Pelham (SNAP-IV) questionnaire, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), the Children's Depression Rating Scale-Revised (CDRS-R), the Giles de la Tourette Syndrome – Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) and the Pediatric Anxiety Rating Scale (PARS). Subjects will be monitored for signs of abuse, and withdrawal or dependence.

Rationale for Amendment

Alternate remote monitoring procedures implemented for safety purposes in response to the COVID-19 pandemic.

To provide investigators guidance to monitor subjects for signs of abuse, and withdrawal or dependence.

Sections: Synopsis/PK and 11.3 Pharmacokinetics Parameters

Existing Text

Blood samples will be collected to measure concentrations of ecopipam and/or its major (active) metabolites at Weeks 4 and 12.

Revised Text

Blood samples will be collected to measure concentrations of ecopipam and/or its major (active) metabolites at Weeks 4 and 12. If visits at Weeks 4 and 12 are not conducted at a site due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event, collection of PK sampling is optional.

Rationale for Amendment

Alternate remote monitoring procedures implemented for safety purposes in response to the COVID-19 pandemic.

Sections: Synopsis/Statistical Methods and 13 Statistics

Existing Text

None

Revised Text

Additional analyses may need to be conducted for data not collected at sites and/or collected via remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event, details of these additional analyses will be specified in the SAP.

Rationale for Amendment

Alternate procedures noted in response to the COVID-19 pandemic.

Section: List of Abbreviations and Definition of Terms

Existing Text

CNS	Central nervous system
C-SSRS	Columbia Suicide Severity Rating Scale

Revised Text

CNS	Central nervous system
COVID-19	SARS-CoV-2 (coronavirus)

Rationale for Amendment

New abbreviation and definition added; incorrect/duplicate abbreviation and definition removed.

Section: 5.2.2.1 Safety in Humans / Study PSY302

Existing Text

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.

Revised Text

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. More patients on placebo had severe adverse events (7.5%) compared to ecopipam (5%).

Rationale for Amendment

Updated information included.

Section: 5.3.1 Assessment of Risk

Existing Text

Of the total human exposures, 540 adults have participated in studies to investigate the safety, tolerability, pharmacodynamics and pharmacokinetics of ecopipam after single and multiple administration. In addition, a total of 2058 adult subjects have received treatment with ecopipam in therapeutic studies, including 1667 with obesity, 279 with cocaine addiction, 56 with schizophrenia, schizoaffective disorder and schizophreniform disorder, 28 with pathological gambling, 1 adult with LND, 18 adults with TS, 40 children/adolescents with TS and 9 adults with stuttering.

Revised Text

Of the 2651 human subjects that have been exposed to ecopipam, 540 adults have participated in studies to investigate the safety, tolerability, pharmacodynamics and pharmacokinetics of ecopipam after single and multiple dose administration. Of the 2651 human subjects that have been exposed to ecopipam, a total of 2058 adult subjects have received treatment with ecopipam in therapeutic studies, including 1667 with obesity, 279 with cocaine addiction, 56 with schizophrenia, schizoaffective disorder and schizophreniform disorder, 28 with pathological gambling, 1 adult with LND, 18 adults with TS, 40 children/adolescents with TS and 9 adults with stuttering.

Rationale for Amendment

Updated information included.

Section: 5.3.3 Methods to Minimize Risks

Existing Text

- All subjects will be evaluated for safety every two weeks while receiving study medication, with 4 evaluations conducted in person and 2 being phone assessments.

Revised Text

- All subjects will be evaluated for safety every two weeks while receiving study medication, with 4 evaluations conducted at the site and 2 via telephone assessments.

Rationale for Amendment

Clarifying language added.

Section: 7.5 Criteria for Study Discontinuation

Existing Text

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

Revised Text

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

Rationale for Amendment

Clarifying language added.

Section: Table 2 Schedule of Assessments

Existing Text

Assessment	Screening[a]	Baseline	Titration		Treatment			Completion/ Early Termination	7 Day Follow-up	14 Day Follow-up	30 day Follow-up*
Study Week	**Up to -4**	**0**	**2***	**4**	**6**	**8**	**10***	**12**	**13/14**	**14/15**	**16/17**
Study Days	**Up to -28**	**0**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**7 Days Post Last Dose ±3**	**14 Days Post Last Dose ±3**	**30 Days Post Last Dose ±3**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Informed Consent	X										
Inclusion/ Exclusion	X	X									
Medical/Psychiatric/medication History	X	X									
Randomization		X									
Physical Exam/Vital Signs[b]	X	X		X	X	X		X	X	X	
ECG	X	X		X	X	X		X	X	X	
Laboratory tests (Hematology and Chemistry)[c]	X	X						X	X	X[c]	
Urine Drug Screen	X	X						X			
Urine Pregnancy Test	X	X						X			
DSM-5 Criteria for TS	X										
Yale Global Tic Severity Scale	X	X		X	X	X		X			
Clinical Global Impression - Tourette's Syndrome of Severity		X		X	X	X		X			

Assessment	Screening[a]	Baseline	Titration		Treatment			Completion/ Early Termination	7 Day Follow-up	14 Day Follow-up	30 day Follow-up*
Study Week	**Up to -4**	**0**	**2***	**4**	**6**	**8**	**10***	**12**	**13/14**	**14/15**	**16/17**
Study Days	**Up to -28**	**0**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**7 Days Post Last Dose ±3**	**14 Days Post Last Dose ±3**	**30 Days Post Last Dose ±3**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Clinical Global Impression - Tourette's Syndrome of Improvement				X	X	X		X			
Caregiver Global Impression of Change				X	X	X		X			
Columbia Suicide Severity Rating Scale	X	X	X	X	X	X	X	X	X	X	
Abnormal Involuntary Movement[d]		X		X	X	X		X			
Barnes Akathisia Rating Scale		X		X	X	X		X			
Swanson, Nolan, and Pelham Questionnaire		X		X	X	X		X			
Children's Yale-Brown Obsessive Compulsive Scale		X		X	X	X		X			
Children's Depression Rating Scale - Revised		X		X	X	X		X			
Gilles de la Tourette Syndrome Quality of Life Scale		X		X	X	X		X			
Pediatric Anxiety Scale		X		X	X	X		X			
PK Blood Draws[e]				X				X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X*
Concomitant Medications	X	X		X	X	X		X	X	X	

Assessment	Screening[a]	Baseline	Titration		Treatment			Completion/ Early Termination	7 Day Follow-up	14 Day Follow-up	30 day Follow-up*
Study Week	**Up to -4**	**0**	**2***	**4**	**6**	**8**	**10***	**12**	**13/14**	**14/15**	**16/17**
Study Days	**Up to -28**	**0**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**7 Days Post Last Dose ±3**	**14 Days Post Last Dose ±3**	**30 Days Post Last Dose ±3**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Dispense Study Drug		X		X	X	X		X[f]			
Collect Unused Study Drug/Assess drug compliance				X	X	X		X	X		

Abbreviations: AE = adverse event; BP = blood pressure; ECG = electrocardiogram; HR = heart rate; PK = pharmacokinetic(s)

[a] Informed consent must be performed prior to any screening procedures. All screening procedures are to occur after washout of any applicable medications. Rescreening is allowed.

[b] Vital signs will include, pulse, BP, orthostatic BP (done 5 minutes after being supine and then 3 minutes after standing), height and weight.

[c] Subjects should be in a fasting state (8 hours) for laboratory tests. HbA1c will be measured at the baseline and completion/early termination visits.

[d] Every attempt should be made to perform this assessment at the same time at each visit.

[e] At Week 4 Study dose should not be taken until after predose blood draw at the site. PK draws should be predose, between 0.5 and 1.5 hours after study drug administration, and between 2 and 4 hours after study drug administration. Both Week 4 and Week 12, visits should be scheduled for the morning. At Week 12, blood sample will be collected in the afternoon at the end of the visit.

[f] Study drug will be dispensed for dose down titration.

* Weeks 2 and 10 will be telephone visits. If there are any abnormal findings, the subject will be brought to the site for full assessment. A telephone call will be made to the subject 30 days after the last dose to assess any adverse events that may have occurred.

Revised Text

Assessment	Screening[a]	Baseline	Titration		Treatment			Completion/ Early Termination	7 Day Follow-up	14 Day Follow-up	30 day Follow-up*
Study Week	**Up to -4**	**0**	**2***	**4[g]**	**6[g]**	**8[g]**	**10***	**12[g]**	**13/14[g]**	**14/15[g]**	**16/17**
Study Days	**Up to -28**	**0**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**7 Days Post Last Dose ±3**	**14 Days Post Last Dose ±3**	**30 Days Post Last Dose ±3**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Informed Consent	X										
Inclusion/ Exclusion	X	X									
Medical/Psychiatric/medication History	X	X									
Randomization		X									
Physical Exam/Vital Signs[b]	X	X		X	X	X		X	X	X	
ECG	X	X		X	X	X		X	X	X	
Laboratory tests (Hematology and Chemistry)[c]	X	X						X	X	X[c]	
Urine Drug Screen	X	X						X			
Urine Pregnancy Test	X	X						X		X	
DSM-5 Criteria for TS	X										
Yale Global Tic Severity Scale	X	X		X	X	X		X			
Clinical Global Impression - Tourette's Syndrome of Severity		X		X	X	X		X			

Assessment	Screening[a]	Baseline	Titration		Treatment			Completion/ Early Termination	7 Day Follow-up	14 Day Follow-up	30 day Follow-up*
Study Week	**Up to -4**	**0**	**2***	**4[g]**	**6[g]**	**8[g]**	**10***	**12[g]**	**13/14[g]**	**14/15[g]**	**16/17**
Study Days	**Up to -28**	**0**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**7 Days Post Last Dose ±3**	**14 Days Post Last Dose ±3**	**30 Days Post Last Dose ±3**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Clinical Global Impression - Tourette's Syndrome of Improvement				X	X	X		X			
Caregiver Global Impression of Change				X	X	X		X			
Columbia Suicide Severity Rating Scale	X	X	X	X	X	X	X	X	X	X	
Abnormal Involuntary Movement[d]		X		X	X	X		X			
Barnes Akathisia Rating Scale		X		X	X	X		X			
Swanson, Nolan, and Pelham Questionnaire		X		X	X	X		X			
Children's Yale-Brown Obsessive Compulsive Scale		X		X	X	X		X			
Children's Depression Rating Scale - Revised		X		X	X	X		X			
Gilles de la Tourette Syndrome Quality of Life Scale		X		X	X	X		X			
Pediatric Anxiety Scale		X		X	X	X		X			
PK Blood Draws[e,h]				X				X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X*
Concomitant Medications	X	X		X	X	X		X	X	X	

Assessment	Screening[a]	Baseline	Titration		Treatment			Completion/ Early Termination	7 Day Follow-up	14 Day Follow-up	30 day Follow-up*
Study Week	**Up to -4**	**0**	**2***	**4[g]**	**6[g]**	**8[g]**	**10***	**12[g]**	**13/14[g]**	**14/15[g]**	**16/17**
Study Days	**Up to -28**	**0**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**7 Days Post Last Dose ±3**	**14 Days Post Last Dose ±3**	**30 Days Post Last Dose ±3**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Dispense Study Drug		X		X	X	X		X[f]			
Collect Unused Study Drug/Assess drug compliance				X	X	X		X	X		

Abbreviations: AE = adverse event; BP = blood pressure; ECG = electrocardiogram; HR = heart rate; PK = pharmacokinetic(s)

[a] Informed consent must be performed prior to any screening procedures. All screening procedures are to occur after washout of any applicable medications. Rescreening is allowed after approval by the Medical Advisor.

[b] Vital signs will include, pulse, BP, orthostatic BP (done 5 minutes after being supine and then 3 minutes after standing), height and weight.

[c] Subjects should be in a fasting state (8 hours) for laboratory tests. HbA1c will be measured at the baseline and completion/early termination visits.

[d] Every attempt should be made to perform this assessment at the same time at each visit.

[e] At Week 4 Study dose should not be taken until after predose blood draw at the site. PK draws should be predose, between 0.5 and 1.5 hours after study drug administration, and between 2 and 4 hours after study drug administration. Both Week 4 and Week 12, visits should be scheduled for the morning. At Week 12, blood sample will be collected in the afternoon at the end of the visit.

[f] Study drug will be dispensed for dose down titration.

* Weeks 2 and 10 will be telephone visits. If there are any abnormal findings, the subject will be brought to the site for full assessment. A telephone call will be made to the subject 30 days after the last dose to assess any adverse events that may have occurred.

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

[h] If visits at Weeks 4 and 12 are completed in locations other than study clinic due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event then collection of labs for PK assessments are optional

Rationale for Amendment

Alternate remote monitoring procedures implemented for safety purposes in response to the COVID-19 pandemic. Note added to indicate that Day 14 Follow Up Visit laboratory results may serve as baseline labs for Study EBS-101-OL-001 to eliminate potential duplicate sampling. Urine pregnancy test added to Day 14 follow up visit to ensure adequate testing of subjects entering into the EBS-101-OL-001 study within 14 days. Clarification regarding approval required for rescreening added.

Section: 8.3 Subject Withdrawal, Removal and Replacement Criteria

Existing Text

Any subject with a CDI assessment indicative of the onset of a new depressive episode at any visit can be discontinued from study participation at the discretion of the Investigator.

Revised Text

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

Rationale for Amendment

Correction of incorrect scale reference.

Section: 10.7 Study Drug Accountability

Existing Text

None

Revised Text

Due to the COVID-19 pandemic, in some cases direct to patient shipments may be necessary. In this case, study medication may be transported to the subject by a third party vendor who has systems in place to protect blinding, patient privacy, and data integrity.

Rationale for Amendment

Modifications implemented as a result of COVID-19 pandemic.

Section: 11 Assessment of Efficacy

Existing Text

None.

Revised Text

Assessments may be completed in locations other than study clinic and/or via remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event.

Rationale for Amendment

Alternate remote monitoring procedures implemented for safety purposes in response to the COVID-19 pandemic.

Sections: Synopsis/Criteria for Evaluation and 11.2 Secondary Efficacy Assessments

Existing Text

Other Secondary efficacy endpoints include:

- Change in Clinician Global Impression Tourette Syndrome of Improvement (CGI-TS-I) from Baseline to Week 12
- Change in YGTSS-Global Score (GS) from Baseline to Week 12
- Change in Caregiver Global Impression of Change (CaGI-C) from Baseline to Week 12

Revised Text

Other Secondary efficacy endpoints include:

- Change in Clinician Global Impression Tourette Syndrome of Improvement (CGI-TS-I) from Week 4 to Week 12
- Change in YGTSS-Global Score (GS) from Baseline to Week 12
- Change in Caregiver Global Impression of Change (CaGI-C) from Week 4 to Week 12

Rationale for Amendment

Efficacy endpoints for Change in Clinician Global Impression Tourette Syndrome of Improvement (CGI-TS-I) and Caregiver Global Impression of Change (CaGI-C) corrected to begin at Week 4 with the first administration of these scales.

Section: 12 Assessment of Safety

Existing Text

None

Revised Text

Assessments may be completed in locations other than study clinic due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event.

Rationale for Amendment

Alternate remote monitoring procedures implemented for safety purposes in response to the COVID-19 pandemic.

Section: 12.1.3 Other Safety Parameters

Existing Text

None

Revised Text

Subjects must be monitored for signs of study drug abuse, and withdrawal or dependence and if detected must be recorded as AEs.

Rationale for Amendment

To provide investigators guidance to monitor subjects for signs of abuse, and withdrawal or dependence.

Section: 13.1 Analysis Population

Existing Text

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.

Revised Text

The list of subjects or observations to be excluded from the PP Population, along with the reason for exclusion, will be finalized prior to database unblinding. Protocol deviations that occur due to the COVID-19 pandemic related issues will be categorized separately as applicable.

Rationale for Amendment

Plan for protocol deviations related to the COVID-19 pandemic specified.

SIGNATURE PAGE

Sponsor's Approval

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

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

Responsible Medical Officer:

PPD

PPD

Date

Drug Development
Emalex Biosciences, Inc.

Sponsor's Authorized Officer:

PPD

PPD

Date

Emalex Biosciences, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for Ecopipam. I have read the protocol EBS-101-CL-001 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Clinical Study Leader	PPD	PPD PPD
Drug Safety Physician	PPD	PPD
24-Hour emergency contact	PPD	PPD

2. SYNOPSIS

Name of Sponsor/Company:
Emalex Biosciences, Inc.

Name of Investigational Product:
Ecopipam Tablets

Protocol Number: EBS-101-CL-001

Title of Study:
A Multicenter, Placebo-Controlled, Double-Blind, Randomized, Parallel-Group, Phase 2b Study to Evaluate the Efficacy and Safety of Ecopipam Tablets in Children and Adolescent Subjects with Tourette's Syndrome

Study center(s): Approximately 60 sites in the United States, Canada, and the European Union

Principal Investigator: TBD
Investigators: TBD

Studied period (years):	**Phase of development:**
Estimated date first subject enrolled: Q2 2019 Estimated date last subject completed: Q2 2022	2b

Objectives:

Primary:

The primary objective of this study is to evaluate the efficacy of ecopipam tablets in pediatric subjects (aged ≥ 6 to <18 years) with Tourette's Syndrome (TS).

Secondary:

The secondary objectives of this study are to evaluate the safety of ecopipam tablets in pediatric subjects (aged ≥ 6 to <18 years) with TS and characterize the pharmacokinetics (PK) of ecopipam.

Exploratory:

To evaluate the PK/pharmacodynamic relationship between plasma levels of ecopipam and treatment effect if possible.

Methodology:

This is a multicenter, placebo-controlled, double-blind, randomized, parallel-group, Phase 2b study in pediatric subjects (aged ≥6 to <18 years) with TS. Following a 28-day Screening period and Baseline visit, eligible subjects will be randomized 1:1 to receive either a target steady-state dose of 2 mg/kg/day ecopipam HCl or matching placebo for a 4-week Titration period followed by an 8-week Treatment period. Following titration, subjects who weigh 18 kg to ≤23 kg will receive a 37.5-mg active dose (or placebo), subjects who weigh >23 kg to ≤34 kg will receive a 50-mg active dose (or placebo), subjects who weigh >34 kg to ≤44 kg will receive a 75-mg active dose (or placebo), subjects who weigh >44 kg to ≤68 kg will receive a 100-mg active dose (or placebo), subjects who weigh >68 kg to ≤83 kg will receive a 150-mg active dose (or placebo), and subjects who weigh >83 kg will receive a 200-mg active dose (or placebo).

After the screening period, subjects will return to the clinic at Baseline and 4, 6, 8 and 12 weeks after Randomization. Study Visits at Weeks 4, 6, 8 and 12 after randomization may be completed in locations other than clinic and/or safety and efficacy assessments required at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event. Subjects will have telephone visits on Weeks 2 and 10 to assess adverse

events and other safety parameters. Efficacy assessments will be conducted at Weeks 4, 6, 8 and 12. Safety assessments will be conducted at these visits as well. A Follow Up visit will be conducted in the clinic 7 and 14 days after the last dose of study medication. The follow up visits on Day 7 and 14 after the last dose of study medication may be completed in locations other than clinic and/or safety and efficacy assessments required at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event. Subjects will also be contacted 30 days after the last dose of study medication to determine any adverse events. At study completion or early termination, subjects will be tapered off study drug as outlined in the protocol.

An interim analysis will be conducted by an independent data safety monitoring board (DSMB) when 50% of the total subjects complete the study. The DSMB will determine the probability of a successful study (conditional power). If this probability is too small and does meet pre-specified criteria, the DSMB could recommend stopping the study for futility. If the probability of a successful study is reasonable, the DSMB can recommend continuing the study as planned. The DSMB can also recommend the continuation of the study with a sample size adjustment based on conditional power.

Sample Size Justification:

A sample size of 75 subjects per group will provide >80% power to detect difference between groups of 3 points on change from baseline the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS), with standard deviation = 6.1 and alpha = 0.05, assuming 10% drop out.

Number of subjects (planned):

75 per arm; 150 total

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1) Subject's parent or legal guardian must sign a written informed consent.
2) Subject must sign a written informed assent according to the requirements of the site's IRB/EC.
3) Subjects must be ≥6 to <18 years of age at time of screening.
4) Subjects must weigh ≥18 kg (39.6 lbs).
5) Subjects must have TS based on Diagnostic and Statistical Manual for Mental Disorders – 5th Edition (DSM-5 diagnostic criteria) for TS.
6) Subjects must exhibit both motor and vocal tics that cause impairment with normal routines.
7) Subjects must have a minimum score of 20 on the YGTSS-TTS at Screening and at Baseline visits with tic symptoms in the investigator's judgment causing:
   a. Subjective discomfort (e.g., pain or injury)
   b. Sustained social problems (e.g., social isolation or bullying)
   c. Social and emotional problems
   d. Functional interference (e.g., impairment of academic achievements)
8) Subjects may not be taking any medications used to treat motor or vocal tics for at least 14 days prior to Baseline.
9) Adolescent females of childbearing potential who are sexually active must be using highly effective contraception (i.e., oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized male partner) and agree to continue use of highly effective contraception for the duration

of their participation in the study. They must also agree to use highly effective contraception for 30 days after their last dose of study drug.

10) Sexually active male subjects must use a highly effective method of contraception during the study and agree to continue the use of highly effective contraception for at least 30 days after the last dose of study drug.
11) For subjects enrolled outside of the United States and Canada, the subject has received an adequate trial of non-pharmacological therapy without adequate response prior to study enrollment as documented by the Investigator.

Exclusion Criteria:

1) Subjects with any unstable primary mood disorder (DSM-5 criteria) at Screening.
2) Subjects who have unstable medical illness or clinically significant abnormalities on laboratory tests, or ECG at Screening as determined by the Principal Investigator.
3) 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'' on any question other than 1–3 (currently or within the past 30 days) on the baseline/screening version of the Columbia Suicide Severity Rating Scale (C-SSRS).
4) Subjects with a clinical presentation at Screening and/or history consistent with another neurologic condition that may have had accompanying abnormal movements (e.g., Huntington's disease, Parkinson's disease, Wilson's disease, stroke, Restless Legs Syndrome).
5) Female subjects who are currently pregnant or lactating or planning to become pregnant during the course of the study.
6) Subjects who have moderate to severe renal insufficiency at Screening.
7) Subjects who have hepatic impairment at Screening
8) Subjects with current or recent (past 3 months) history of DSM-5 substance use disorder (with the exception of nicotine).
9) Subjects with positive urine drug screen for cocaine, amphetamine, methamphetamine, benzodiazepines, barbiturates, phencyclidine (PCP), or opiates at Screening, except those receiving stable, prescribed treatment for attention deficit/hyperactivity disorder (ADHD)
10) Subjects with a $\geq$ 25% difference in the absolute change in YGTSS-TTS score between the Screening visit and the Baseline visit
11) Subjects with a lifetime history of bipolar disorder type I or II, dementia, schizophrenia, or any other psychotic disorder.
12) Subjects with a major depressive episode in the past 2 years.
13) Subjects with a history of attempted suicide.
14) Subjects with a history of seizures (excluding febrile seizures that occurred <2 years prior to Screening).
15) Subjects with a history of neuroleptic malignant syndrome.
16) Subjects with a myocardial infarction within 6 months.
17) Subjects who have had previous treatment with ecopipam.
18) Subjects who have had previous treatment with:
    - investigational medication within 1 month prior to Screening
    - depot neuroleptics within 3 months prior to Screening
    - oral neuroleptics within 4 weeks prior to Screening
19) Subjects receiving anti-depressant, anti-anxiety or anti-ADHD medications unless the dosage has been stable for a minimum of 4 weeks prior to Screening and not prescribed to relieve the neurological symptoms related to TS.

20) 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.
21) Initiation or changes in behavioral therapies for TS during the course of the study (i.e., Habit Reversal Training or Comprehensive Behavioral Intervention for Tics) as well as deep brain stimulation.
22) Subjects who have initiated new behavioral therapies fewer than 10 weeks prior to Baseline visit
23) Subjects unable to swallow tablets
24) Subjects with a known hypersensitivity to ecopipam or any of its excipients.
25) Any subject who in the opinion of the investigator is not a suitable candidate for the study.

Investigational product, dosage and mode of administration:

Ecopipam HCl 12.5-, 50-, 75- and 100-mg tablets; 2 mg/kg/day target dose; oral administration.

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

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

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

During the 8-week treatment phase, the following ecopipam HCl doses or matching placebo will be administered for each of the weight bands:

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

All doses will be administered once daily in the evening.

At the end of the 8-week treatment phase, subjects will titrate off therapy and receive ecopipam HCl doses or matching placebo that will be reduced by 25 mg/day until off of drug; signs of symptoms of withdrawal will be monitored.

Duration of treatment:

Four weeks Screening Phase, Baseline Visit, 4-week Titration Period, 8-week Treatment Period and 2-week Follow-up Period. There will also be a phone call to subjects 30 days after study completion or early termination to assess any adverse events.

Reference therapy, dosage, and mode of administration:

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

Criteria for evaluation:

Efficacy:

Primary Efficacy Endpoint:

The primary efficacy endpoint is the change in the Yale Global Tic Severity Scale – Total Tic Score (YGTSS-TTS, i.e., sum of the motor and phonic tic scores) from baseline (YGTSS-TTS score from Baseline visit) to end of therapy (YGTSS-TTS score from Week 12).

Key Secondary Efficacy Endpoint:

- Change in Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) from Baseline to Week 12

Other Secondary efficacy endpoints include:

- Change in Clinician Global Impression Tourette Syndrome of Improvement (CGI-TS-I) from Week 4 to Week 12
- Change in YGTSS-Global Score (GS) from Baseline to Week 12
- Change in Caregiver Global Impression of Change (CaGI-C) from Week 4 to Week 12
- Change in Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) from Baseline to Week12
- Percentage of subjects with a 25% improvement on the YGTSS-TTS
- Percentage of subjects with complete remission of tics on the YGTSS-TTS
- Change in YGTSS-TTS from Baseline to Weeks 4, 6, and 8
- Change in CGI-TS-S from Baseline to Weeks 4, 6, and 8
- Change in CGI-TS-I from Baseline to Weeks 4, 6, and 8
- Change in YGTSS-GS from Baseline to Weeks 4, 6, and 8
- Change in CaGI-C from Baseline to Weeks 4, 6, and 8
- Change in the C&A-GTS-QOL from Baseline to Weeks 4, 6, and 8

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

Safety:

Study Visits at Weeks 4, 6, 8 and 12 after randomization may be completed in locations other than clinic and/or safety assessments required at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event. Safety will be 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 the baseline and completion/early termination visits. Regular measurement of vital signs and the performance of a physical examination and an ECG will occur at Screening, Baseline and Weeks 4, 6, 8 and 12 and 7 and 14 day Follow Up visits. An additional assessment will include the Columbia-

Suicide Severity Rating Scale (C-SSRS) (all Visits except 30 day Follow up visit). Additional safety outcomes (Baseline and Weeks 4, 6, 8 and 12) will include the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Swanson, Nolan and Pelham (SNAP-IV) questionnaire, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), the Children's Depression Rating Scale-Revised (CDRS-R), the Giles de la Tourette Syndrome – Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) and the Pediatric Anxiety Rating Scale (PARS). Subjects will be monitored for signs of abuse, and withdrawal or dependence.

PK:

Blood samples will be collected to measure concentrations of ecopipam and/or its major (active) metabolites at Weeks 4 and 12. If visits at Weeks 4 and 12 are not conducted at a site due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event, collection of PK samples is optional.

For the Week 4 visit, a morning appointment is suggested. Parents/caregivers will be instructed not to administer the study medication to the subject on the evening prior to the Week 4 visit and to record the time of administration of the last dose of study medication taken. The study drug administration will occur on the day of the Week 4 visit at the site under the supervision of the study investigator. An intravenous catheter will be placed, and the subject will have samples collected at the following time windows: one sample at pre-dose (34 to 44 hours since the last dose), one sample between 0.5 and 1.5 hour after administration of study medication, and one sample between 2 and 4 hours after study drug administration. Any samples should be collected at least 30 min apart.

For the Week 12 visit, parents/caregivers will be asked to record the time of study drug administration on the evening prior to the visit. An appointment is suggested to be made for the morning of the Week 12 visit. A blood sample will be collected at the end of the visit. The time of sample collection will be recorded. Blood samples will be processed as outlined in the protocol and serum/plasma will be frozen, shipped and analyzed for ecopipam and SCH40853.

Statistical methods:

Efficacy:

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

The primary efficacy endpoint for this study will be the change from Baseline (YGTSS-TTS from Baseline) to end of therapy (YGTSS-TTS from Week 12).

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

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

Additional analyses may need to be conducted for data not collected at sites and/or collected via remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event, details of these additional analyses will be specified in the SAP.

The full details will be specified in the SAP.

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 separately, using data from this study along with data from adults using the same tablet formulation (if available). The methodology for analyses will be reported in a separate analysis plan.

3. TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviations	Terms
ADD	Attention Deficit Disorder
ADHD	attention deficit/hyperactivity disorder
ADL	Activities of Daily Living
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AMP	adenosine monophosphate
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
AUC	area under the plasma-concentration time course profile
$AUC_{(0\text{-}24\ hr)}$	area under the plasma-concentration time course profile from time 0 (dosing) to 24 hours after dosing
BUN	blood urea nitrogen
C&A-GTS-QOL	Child and Adolescent Gilles De La Tourette Syndrome-Quality of Life Scale
CaGI-C	Caregiver Global Impression of Change
CFR	Code of Federal Regulations
CDI	Children's Depression Inventory
CDRS-R	Children's Depression Rating Scale-Revised
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
CGI	Clinical Global Impression
CGI-TS-I	Clinical Global Impression Tourette's Syndrome of Improvement
CGI-TS-S	Clinical Global Impression Tourette's Syndrome of Severity
C_{max}	maximum observed concentration
CNS	Central nervous system
COVID-19	SARS-CoV-2 (coronavirus)
CRA	Clinical research associate
CRO	Clinical research organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTC	Common Toxicity Criteria
CV	coefficient of variation
C-YBOCS	Child Yale-Brown Obsessive Compulsive Scale
DCI	Diagnostic Confidence Index
DSM-5 CC-SM	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition Cross-Cutting Symptom Measures
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EEG	Electroencephalogram
FDA	Food and Drug Administration

GCP	Good Clinical Practices
GS	Global score
HCl	Hydrochloride
123I-β-CIT SPECT	(2β-carbomethoxy-3β-[4-iodophenyl]tropane) single photon emission computed tomography
HbA1c	Hemoglobin A1c
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous
Ki	Inhibition constant
LDH	lactate dehydrogenase
LFT	Liver function test(s)
LND	Lesch-Nyhan Disease
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OCD	Obsessive-Compulsive Disorder
PARS	Pediatric Anxiety Rating Scale
PCP	Phencyclidine
PET	Positron emission tomography
PO	Oral (per os)
QD	Once daily
SAE	serious adverse event
SC	Subcutaneous
SCH	Schering-Plough drug code indicator
SNAP-IV	Swanson, Nolan, and Pelham questionnaire
t_{max}	time from dosing to the maximum observed concentration
TS	Tourette's Syndrome
TTS	Total Tic Score
US	United States
YGTSS-TTS	Yale Global Tic Severity Scale-Total Tic Score

5. INTRODUCTION

5.1 Background on Tourette's Syndrome

Tourette's Syndrome (TS) is a neurological disorder characterized by motor or vocal tics that begin in childhood and persist over time (see box below with the Diagnostic and Statistical Manual for Mental Disorders – 5th Edition [DSM-5 diagnostic criteria). The tics are brief in duration, occur spontaneously, and do not show a regular temporal pattern. Further the tics are not caused by medications, other medical reasons, or confirmed neurological abnormality. They can be consciously suppressed for some time and are exacerbated by stress. Males are more susceptible than females with a ratio of about 4.1 to 3. Motor tics can include such things as eye-blinking, facial grimacing, mouth movements, head jerks, shoulder shrugs and arm/leg jerks. In more severe cases gyrating, bending, pivoting and dystonic movements are possible. Vocal tics are fast meaningless sounds or noises, and include such things as sniffing, throat clearing, grunting, barks and squealing. Complex vocal tics can include shouting out of single words, whole sentences or repeating words (echolalia). In small numbers of subjects, explosive obscenities (coprolalia) are possible.[1,2] Diagnosis of TS is complicated because it often co-exists with other psychiatric illnesses. Common co-morbid conditions include attention deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, and depression.[2] These symptoms often mask TS and make diagnosis difficult. Tic severity can range from mild to severe according to its frequency and intensity. The tics have a variable course, with severe bouts interspersed with complete absence of symptoms. Onset of tics is seen early in childhood (average approximately 7 years) and peaks in the teenage years. Vocal tics appears several years after the onset of motor tics. For most subjects, the period of worst-ever tic severity is between 7 and 15 years of age, followed by a steady decline in tic severity. As subjects mature, the vast majority of tics will disappear permanently, with a small percentage of subjects having tics that persist into adulthood and require treatment. Complete remission of tics is reported in approximately 50% of subjects. Severe tics are thought to occur only in about 10% of the cases.[3]

DSM-5 Diagnostic Criteria For Tourette's Syndrome

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

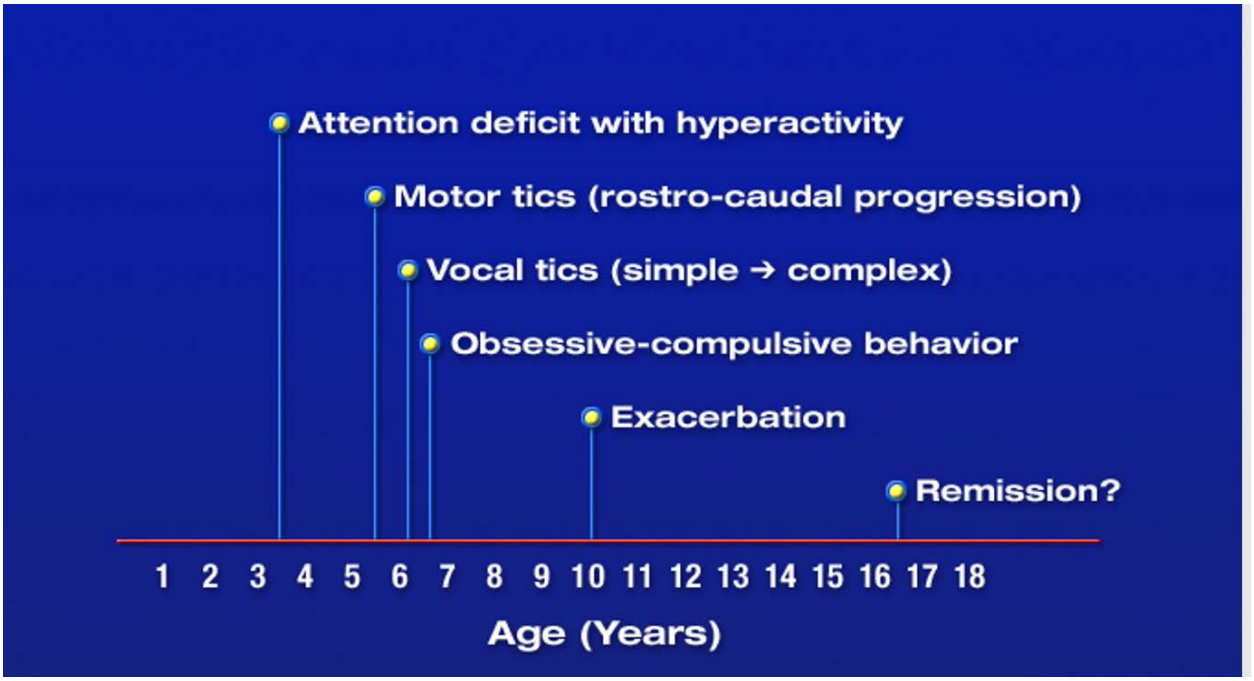
A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.

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

C. The onset is before age 18 years.

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

Natural History of Tics



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

5.1.1. Disrupted Dopamine Systems in Tourette's Syndrome

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

- Dopamine-rich areas of the brain (e.g., striatum) are believed to control motor tics.
- Clinical neuroimaging studies of TS subjects implicate dopamine-rich brain areas.

- Dopamine antagonists can ameliorate tics.
- Catecholamine depletors (e.g., tetrabenazine) can ameliorate tics.

5.2. Background on Ecopipam

CCI

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

5.2.2. Clinical Data

5.2.2.1. Safety in Humans

Clinical Summary: Legacy Schering-Plough Studies in Indications other than TS

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 I clinical studies was somnolence. Other commonly reported adverse events in Phase I 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 HCl showed a dose-dependent weight loss. These 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 HCl 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 HCl 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.

Clinical Summary: Legacy Psyadon Studies in Indications other than TS

Following acquisition of ecopipam by Psyadon from Schering-Plough, two Phase 1 studies, one study in Lesch-Nyhan Disease (LND) subjects aged ≥6 years old (PSY101) and one study of the 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 (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 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 LND 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.

Clinical Summary: Psyadon Clinical Studies in TS Subjects

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

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 primary outcome measure was Yale Global Tic Severity Scale (YGTSS). After ecopipam treatment, YGTSS total scores, motor tics scores, phonic tics scores and overall impairment were all significantly decreased from baseline to endpoint, which indicated that the severity of tics was

decreased. 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 up to 50 mg/day (if <75 lbs) or 100 mg/day (if >75 lbs) for four weeks. The primary endpoint was the YGTSS Total (MP) Scores which were the sum of the motor and phonic subscales of YGTSS. In the ITT population, the mean (±SD) YGTSS Total (MP) Scores at baseline were 32.8 (±7.1) prior to ecopipam treatment and 33.7 (±6.7) prior to placebo treatment. On Day 16 of the treatment period, YGTSS Total (MP) Scores decreased 5.1 (±8.5) points on ecopipam and 2.1(±4.7) points on placebo. On Day 30, YGTSS Total (MP) Scores decreased 5.5 (±8.7) points on Ecopipam and 3.4 (±5.8) points on placebo. Similar results were observed in the Evaluable population.

In the ITT population, LS means (±SE) of the difference between ecopipam and placebo treatment were -2.8885±1.5282 (95%CI: -5.9822, 0.2053, p=0.0664) on Day 16 and -2.1366 ±1.6551 (95%CI: -5.4871, 1.2139, p=0.2045) on Day 30. The treatment difference was more obvious in the evaluable population for both dates (on Day 16, p=0.0155, and on Day 30, p=0.0435).

With respect to secondary endpoints, the changes of subscale scores were similar to YGTSS Total (MP) Scores results. In the ITT population, the mean (±SD) motor, phonic, impairment and global scores (the sum of motor, phonic and impairment scores) at baseline were 18.4 (±3.3), 14.4 (±4.9), 28.0 (±10.7) and 60.8 (±16.5) prior to ecopipam, and 18.3 (±3.4), 15.4 (±4.5), 27.5 (±9.3) and 61.2 (±14.0) prior to placebo, respectively. After 30-day treatment, the decreases in scores compared to baseline were 3.3 (±4.2), 2.3 (±4.9), 7.0 (±11.6) and 12.6 (±18.7) on ecopipam and 1.6 (±3.3), 1.8 (±3.6), 3.0 (±9.1) and 6.4 (±13.4) on placebo, respectively. Similar results were observed in evaluable population.

In the ITT population, after 30-days of treatment, CGI Severity Scores decreased 0.8 (±0.7) points on ecopipam and 0.2 (±0.9) points on placebo. Also, after ecopipam treatment, the percentages of subjects with much improved, minimally improved, no change, minimally worse CGI Improvement ratings were 40.00%, 15.00%, 20.00% and 12.5%, while the percentages on placebo were 20.00%, 27.50%, 32.50% and 12.50%, respectively. Similar results were observed in evaluable population. These data suggest that the subjects' disease severity decreased and that they had greater improvement while on ecopipam.

In the ITT population, the mean (±SD) DuPaul ADHD rating scale at baseline was 20.2 (±11.6) points prior to ecopipam and 22.1 (±11.3) points prior to placebo. On Day 30, ADHD scores decreased 1.9 (±5.2) points on ecopipam and 2.7 (±6.6) points on placebo. ADHD scales were almost unchanged after ecopipam treatment. Similar results were observed in evaluable population.

In the ITT population, the mean (±SD) YBOCS total scores at baseline were 5.7 (±6.3) prior to ecopipam and 6.6 (±6.9) prior to placebo. On Day 30 of the treatment period, YBOCS total scores decreased 0.8 (±3.3) points on ecopipam and 0.9(±4.1) points on placebo. The results of obsession and compulsion subscales were similar to the total scores.

The safety population was the same as the ITT population.

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. More patients on placebo had severe adverse events (7.5%) compared to ecopipam (5%). 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 one day 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, 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.

5.3. Risk-Benefit Assessment

A consideration of the potential of risks that TS subjects may be exposed to, approaches to reducing any such risks, and the possible benefits that they may derive from their participation in EBS-101-CL-001 is outlined below.

5.3.1. Assessment of Risk

As 2651 human subjects have been exposed to single and multiple doses of ecopipam and safety data including collection of adverse events, physical examinations, laboratory tests, ECGs etc. have been systematically collected, there exists a fair body of information to base the understanding of potential risks and approaches to minimizing them in current and future studies.

Of the 2651 human subjects that have been exposed to ecopipam, 540 adults have participated in studies to investigate the safety, tolerability, pharmacodynamics and pharmacokinetics of ecopipam after single and multiple dose administration. Of the 2651 human subjects that have been exposed to ecopipam, a total of 2058 adult subjects have received treatment with ecopipam in therapeutic studies, including 1667 with obesity, 279 with cocaine addiction, 56 with schizophrenia, schizoaffective disorder and schizophreniform disorder, 28 with pathological gambling, 1 adult with LND, 18 adults with TS, 40 children/adolescents with TS and 9 adults with stuttering. These have shown that ecopipam is generally well tolerated with the adverse events affecting primarily the CNS (e.g., sedation, insomnia, psychiatric changes such as depression, anxiety and suicidal ideation) and the gastrointestinal system (e.g., nausea and vomiting).

In subjects with TS, ecopipam has been evaluated in two studies, one study in adult subjects with TS and one study in children/adolescents with TS. In the pediatric TS study, overall, adverse events were more common in ecopipam compared to placebo. There were no serious adverse events (SAEs) and only one subject discontinued treatment due to an adverse event in the ecopipam group. Most adverse events were mild to moderate in severity. Adverse events in the Psychiatric Disorders, Central Nervous System Disorders and Gastrointestinal Disorders categories were more common with ecopipam than placebo. Notably, more subjects experienced adverse events of somnolence, insomnia, sedation, restlessness, irritability, nausea and vomiting with ecopipam than with placebo. There were no AEs of extra-pyramidal symptoms in the pediatric study. A higher percentage of subjects on ecopipam gained 5 pounds or more during the study than with placebo (17.5% compared to 15%). Orthostatic blood pressure assessments were not done (or not reported). A table of weight changes was provided for the open-label extension study (PSY302A) and almost all of the children gained weight after 3, 6, 9 or 12 months of treatment. Suicidal ideation was seen both during the blinded study as well as the open-label extension study in pediatric subjects ecopipam. There did not appear to be clinically significant ECG findings. However, open-label extension adverse event data have not yet been analyzed.

In the adult study in TS, 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%). Two subjects developed adverse event of akathisia and one developed an adverse event of tremor, both of which are extrapyramidal reactions. Three of 18 subjects (16.7%) also discontinued study drug due to an adverse event.

For the older obesity and cocaine dependence program, there were subjects who experienced adverse events of weight gain, suicidal ideation, diabetes, extrapyramidal reactions, somnolence, insomnia, hypotension and sexual side effects. There was no raw data on orthostatic blood pressure. In a table of all adverse events during the whole program, the adverse event of dyskinesia is listed but is not in any of the data tables. When reviewing the large Phase 2 and Phase 3 studies in obesity and the other indications, the rate of tardive dyskinesia appears to be extremely low (or absent) and the rate of other extrapyramidal reactions (akathisia, tremor, etc.) appears at rates that are largely less than what is seen with D1/D2 antagonists. Data for shifts in fasting glucose or lipids were not in the Investigator's Brochure prepared by a previous sponsor and comments were made that there were no significant laboratory changes. There did not appear to be a high rate of increased blood glucose or lipids in the adverse event tables for the other studies. Additionally, data on orthostatic blood pressure changes were not documented but no adverse events of orthostatic hypotension were observed.

5.3.2. Assessment of Benefit

A review of the efficacy evaluations for ecopipam in the two studies conducted in subjects with TS reveals improvement on the YGTSS scores and other measures of illness severity from baseline to end point.

In a Phase 2a, open-label, non-randomized study (PSY301), the activity and safety of ecopipam in 18 adult subjects with TS was evaluated. Subjects were to receive ecopipam HCl 50 mg for 2 weeks followed by 100 mg for 6 weeks. The primary outcome measure was the YGTSS Total (MP) score. After ecopipam treatment, the YGTSS Total score, motor tics score, phonic tics

score and overall impairment decreased from baseline to endpoint, suggesting that the severity of tics was decreased (Table 16, Investigator's Brochure).

In a Phase 2b double-blind, randomized crossover study in children/adolescents (ages 7-17 years) with TS (PSY302), 40 subjects were enrolled and 38 (95.0%) completed the study. The primary endpoint was the YGTSS Total (MP) score.

Ecopipam treatment resulted in a numerical decrease in the YGTSS Total score relative to the placebo treatment, but the decrease was not statistically significant (Figure 9, Investigator's Brochure). The least squares means (±SE) of the difference between ecopipam and placebo treatment were -2.8885 (±1.5282); 95% CI: -5.9822, 0.2053, p=0.0664) on Day 16 and -2.1366 (±1.6551; 95% CI: -5.4871, 1.2139, p=0.2045) on Day 30.

Based on the available safety data, there are some safety advantages for ecopipam compared to D2 antagonists, but the full measure of differentiation will not be known until after a larger and longer Phase 3 program. The rate of tardive dyskinesia and other extrapyramidal reactions commonly associated with D2 antagonists appears much lower with ecopipam. Other possible advantages include a decreased risk of lipid changes, hyperglycemia and orthostatic hypotension.

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

5.3.3. Methods to Minimize Risks

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

- Subjects will be screened for appropriateness to participate in the study.
- All subjects will be evaluated for safety every two weeks while receiving study medication, with 4 evaluations conducted at the site and 2 via telephone assessments.
- All subjects will be evaluated using the following scales to assess possible worsening of other psychiatric symptoms or other side effects:
  - Abnormal Involuntary Movements Scale
  - Barnes Akathisia Rating Scale
  - Caregiver Global Impression of Change
  - Columbia Suicide Severity Rating Scale
  - Children's Depression Rating Scale
  - Children's Yale-Brown Obsessive Compulsive Scale
  - Gilles de la Tourette Syndrome Quality of Life Scale
  - Pediatric Anxiety Scale
  - Swanson, Nolan and Pelham Questionnaire

In summary, ecopipam is a new chemical entity with a novel mechanism of action that has some evidence that it may be of therapeutic benefit to subjects with TS. There is also evidence that it is likely to have lower side effect burden (for movement disorders, extra-pyramidal symptoms, tardive dyskinesia, etc., metabolic syndrome and elevated prolactin) than the currently used dopamine antagonists. The protocol has processes to minimize potential risks from study medication that participants may be exposed to such that risks from the study balance the potential benefits.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of ecopipam tablets in pediatric subjects (aged ≥6 to <18 years) with Tourette's Syndrome (TS).

6.2. Secondary Objectives

The secondary objectives of this study are to evaluate the safety of ecopipam tablets in pediatric subjects (aged ≥6 to <18 years) with TS and characterize the pharmacokinetics (PK) of ecopipam.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2b study in pediatric subjects (aged ≥6 to <18 years) with TS. Following a Screening period up to 28 days and Baseline visit, eligible subjects will be randomized 1:1 to receive either a target steady-state dose of 2 mg/kg/day ecopipam HCl or matching placebo for a 4-week Titration period followed by an 8-week Treatment period. Following titration, subjects who weigh ≥18 kg to ≤23 kg will receive a 37.5-mg active dose (or placebo), subjects who weigh >23 kg to ≤34 kg will receive a 50-mg active dose (or placebo), subjects who weigh >34 kg to ≤44 kg will receive a 75-mg active dose (or placebo), subjects who weigh >44 kg to ≤68 kg will receive a 100-mg active dose (or placebo), subjects who weigh >68 kg to ≤83 kg will receive a 150-mg active dose (or placebo), and subjects who weigh >83 kg will receive a 200-mg active dose (or placebo).

After the Screening period, subjects will return to the clinic at Baseline and at 4, 6, 8, and 12 weeks after Randomization. Study visits at Weeks 4, 6, 8 and 12 after randomization may be completed in locations other than clinic and/or safety and efficacy assessments required at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event. Subjects will have telephone visits on Weeks 2 and 10 to assess adverse events and other safety parameters. Efficacy assessments will be conducted at Weeks 4, 6, 8, and 12, and safety assessments will be conducted at all visits as well. A Follow Up visit will be conducted in the clinic 7 and 14 days after the last dose of study medication. The follow up visits on Day 7 and 14 after the last dose of study medication may be completed in locations other than clinic and required assessments at these visits will be made available for remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event. Subjects will also be contacted 30 days after the last dose of study medication to determine any adverse events. At study completion or early termination, subjects will be tapered off study drug as outlined in the protocol.

7.2. Number of Subjects

One hundred and fifty subjects will participate in the study.

7.3. Treatment Assignment

Subjects will be randomized 1:1 to either ecopipam or matching placebo. Randomization assignment will be stratified by weight.

7.4. Dose Adjustment Criteria

Doses will be titrated up to and down from the target dose based on the subject's weight at Baseline according to the following weight bands to better achieve the targeted 2 mg/kg/day target dose: ≥18 to ≤23 kg, >23 to ≤34 kg, >34 to ≤44 kg, >44 to ≤68 kg, >68 to ≤83 kg, >83 kg. Those who cannot tolerate the target dose will be withdrawn from study. Weight band assignments will not change during the duration of the study. See Section 10.5 for direction on administration of study drug.

7.5. Criteria for Subject Study Discontinuation

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

Any subject with a new positive response on questions 4 and/or 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) will be immediately discontinued and evaluated for risk. Dosing may be restarted at the discretion of the Investigator following consultation with the Sponsor or its designee.

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

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

Table 2: Schedule of Assessments

Assessment	Screening[a]	Baseline	Titration		Treatment			Completion/ Early Termination	7 Day Follow-up	14 Day Follow-up	30 day Follow-up*
Study Week	**Up to -4**	**0**	**2***	**4[g]**	**6[g]**	**8[g]**	**10***	**12[g]**	**13/14[g]**	**14/15[g]**	**16/17**
Study Days	**Up to -28**	**0**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**7 Days Post Last Dose ±3**	**14 Days Post Last Dose ±3**	**30 Days Post Last Dose ±3**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Informed Consent	X										
Inclusion/ Exclusion	X	X									
Medical/Psychiatric/medication History	X	X									
Randomization		X									
Physical Exam/Vital Signs[b]	X	X		X	X	X		X	X	X	
ECG	X	X		X	X	X		X	X	X	
Laboratory tests (Hematology and Chemistry)[c]	X	X						X	X	X[c]	
Urine Drug Screen	X	X						X			
Urine Pregnancy Test	X	X						X		X	
DSM-5 Criteria for TS	X										
Yale Global Tic Severity Scale	X	X		X	X	X		X			
Clinical Global Impression - Tourette's Syndrome of Severity		X		X	X	X		X			
Clinical Global Impression - Tourette's Syndrome of Improvement				X	X	X		X			

Assessment	Screening[a]	Baseline	Titration		Treatment			Completion/ Early Termination	7 Day Follow-up	14 Day Follow-up	30 day Follow-up*
Study Week	**Up to -4**	**0**	**2***	**4[g]**	**6[g]**	**8[g]**	**10***	**12[g]**	**13/14[g]**	**14/15[g]**	**16/17**
Study Days	**Up to -28**	**0**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**7 Days Post Last Dose ±3**	**14 Days Post Last Dose ±3**	**30 Days Post Last Dose ±3**
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Caregiver Global Impression of Change				X	X	X		X			
Columbia Suicide Severity Rating Scale	X	X	X	X	X	X	X	X	X	X	
Abnormal Involuntary Movement[d]		X		X	X	X		X			
Barnes Akathisia Rating Scale		X		X	X	X		X			
Swanson, Nolan, and Pelham Questionnaire		X		X	X	X		X			
Children's Yale-Brown Obsessive Compulsive Scale		X		X	X	X		X			
Children's Depression Rating Scale - Revised		X		X	X	X		X			
Gilles de la Tourette Syndrome Quality of Life Scale		X		X	X	X		X			
Pediatric Anxiety Scale		X		X	X	X		X			
PK Blood Draws[e,h]				X				X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X*
Concomitant Medications	X	X		X	X	X		X	X	X	
Dispense Study Drug		X		X	X	X		X[f]			

Assessment	Screening[a]	Baseline	Titration		Treatment			Completion/ Early Termination	7 Day Follow-up	14 Day Follow-up	30 day Follow-up*
Study Week	**Up to -4**	**0**	**2***	**4[g]**	**6[g]**	**8[g]**	**10***	**12[g]**	**13/14[g]**	**14/15[g]**	**16/17**
Study Days	**Up to -28**	**0**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**7 Days Post Last Dose ±3**	**14 Days Post Last Dose ±3**	**30 Days Post Last Dose ±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; ECG = electrocardiogram; HR = heart rate; PK = pharmacokinetic(s)

[a] Informed consent must be performed prior to any screening procedures. All screening procedures are to occur after washout of any applicable medications. Rescreening is allowed after approval by the Medical Advisor.

[b] Vital signs will include, pulse, BP, orthostatic BP (done 5 minutes after being supine and then 3 minutes after standing), height and weight.

[c] Subjects should be in a fasting state (8 hours) for laboratory tests. HbA1c will be measured at the baseline and completion/early termination visits.

[d] Every attempt should be made to perform this assessment at the same time at each visit.

[e] At Week 4 Study dose should not be taken until after pre-dose blood draw at the site. PK draws should be pre-dose, between 0.5 and 1.5 hours after study drug administration, and between 2 and 4 hours after study drug administration. Both Week 4 and Week 12, visits should be scheduled for the morning. At Week 12, blood sample will be collected in the afternoon at the end of the visit.

[f] Study drug will be dispensed for dose down titration.

* Weeks 2 and 10 will be telephone visits. If there are any abnormal findings, the subject will be brought to the site for full assessment. A telephone call will be made to the subject 30 days after the last dose to assess any adverse events that may have occurred.

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

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Inclusion Criteria

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

1) Subject's parent or legal guardian must sign a written informed consent.
2) Subject must sign a written informed assent according to the requirements of the site's IRB/EC.
3) Subjects must be ≥6 to <18 years of age at time of screening.
4) Subjects must weigh ≥18 kg (39.6 lbs).
5) Subjects must have TS based on Diagnostic and Statistical Manual for Mental Disorders – 5th Edition (DSM-5 diagnostic criteria) for TS.
6) Subjects must exhibit both motor and vocal tics that cause impairment with normal routines.
7) Subjects must have a minimum score of 20 on the YGTSS-TTS at Screening and at Baseline visits with tic symptoms in the Investigator's judgment causing:
    a. Subjective discomfort (e.g., pain or injury)
    b. Sustained social problems (e.g., social isolation or bullying)
    c. Social and emotional problems
    d. Functional interference (e.g., impairment of academic achievements)
8) Subjects may not be taking any medications used to treat motor or vocal tics for at least 14 days prior to Baseline.
9) Adolescent females of childbearing potential who are sexually active must be using highly effective contraception (i.e., oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized male partner) and agree to continue use of highly effective contraception for the duration of their participation in the study. They must also agree to use highly effective contraception for 30 days after their last dose of study drug.
10) Sexually active male subjects must use a highly effective method of contraception during the study and agree to continue the use of highly effective contraception for at least 30 days after the last dose of study drug.
11) For subjects enrolled outside of the United States and Canada, the subject has received an adequate trial of non-pharmacological therapy without adequate response prior to study enrollment as documented by the Investigator.

8.2. Exclusion Criteria

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

1) Subjects with any unstable primary mood disorder (DSM-5 criteria) at Screening.

2) Subjects who have unstable medical illness or clinically significant abnormalities on laboratory tests, or ECG at Screening as determined by the Principal Investigator.
3) 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" on any question other than 1–3 (currently or within the past 30 days) on the baseline/screening version of the C-SSRS.
4) Subjects with a clinical presentation at Screening and/or history consistent with another neurologic condition that may have had accompanying abnormal movements (e.g., Huntington's disease, Parkinson's disease, Wilson's disease, stroke, Restless Legs Syndrome).
5) Female subjects who are currently pregnant or lactating or planning to become pregnant during the course of the study.
6) Subjects who have moderate to severe renal insufficiency at Screening.
7) Subjects who have hepatic impairment at Screening.
8) Subjects with current or recent (past 3 months) history of DSM-5 substance use disorder (with the exception of nicotine).
9) Subjects with positive urine drug screen for cocaine, amphetamine, methamphetamine, benzodiazepines, barbiturates, phencyclidine (PCP) or opiates at Screening except those receiving stable, prescribed treatment for ADHD.
10) Subjects with $\geq$ 25% absolute change in YGTSS-TTS score between the Screening Visit and Baseline visit assessments.
11) Subjects with a lifetime history of bipolar disorder type I or II, dementia, schizophrenia, or any other psychotic disorder.
12) Subjects with a major depressive episode in the past 2 years.
13) Subjects with a history of attempted suicide.
14) Subjects with a history of seizures (excluding febrile seizures that occurred <2 years prior to Screening).
15) Subjects with history of neuroleptic malignant syndrome.
16) Subjects with a myocardial infarction within 6 months.
17) Subjects who have had previous treatment with ecopipam.
18) Subjects who have had previous treatment with:
    a. investigational medication within 1 month prior to Screening
    b. depot neuroleptics within 3 months prior to Screening
    c. oral neuroleptics within 4 weeks prior to Screening
19) Subjects receiving anti-depressant, anti-anxiety or anti-ADHD medications unless the dosage has been stable for a minimum of 4 weeks prior to Screening and not prescribed to relieve the neurological symptoms related to TS.
20) 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.
21) Initiation or changes in behavioral therapies for TS during the course of the study (i.e., Habit Reversal Training or Comprehensive Behavioral Intervention for Tics) as well as deep brain stimulation.
22) Subjects who have initiated new behavior therapies fewer than 10 weeks prior to Baseline visit.

23) Subjects unable to swallow tablets.
24) Subjects with a known hypersensitivity to ecopipam or any of its excipients.
25) Any subject who in the opinion of the investigator is not a suitable candidate for the study.

8.3. Subject Withdrawal, Removal, and Replacement Criteria

Any subject with a CDRS-R assessment indicative of the onset of a new depressive episode at any visit can be discontinued from study participation at the discretion of the Investigator. Any subject with a new positive response on questions 4 and/or 5 of the C-SSRS will be immediately discontinued and evaluated for risk. Dosing may be restarted at the discretion of the Investigator following consultation with the Sponsor or its designee.

The Investigator or subject may choose to stop study treatment at any time for safety or personal reasons.

Where possible, a subject who discontinues treatment will undergo protocol-specified end-of study procedures at the time of discontinuation. Date and reason(s) of premature discontinuation will be described in the CRF. In addition, the date of last dose of study treatment will be recorded on the Study Treatment Dosing CRF.

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

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

Table 3: Investigational Product

	Investigational Product	
Product Name	Ecopipam HCl	Placebo
Dosage Form	Tablets	Matching Tablets
Unit Dose of Ecopipam HCl	12.5, 50, 75 and 100 mg	Matching unit dose tablets
Route of Administration	Oral	Oral
Physical Description	Round, biconvex, light blue film-coated tablet, plain on both side	Round, biconvex, light blue film-coated tablet, plain on both sides
Manufacturer	Corealis Pharma Inc	Corealis Pharma Inc

9.2. 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. Nonpharmacologic therapies/procedures will also be captured on the CRF. The Investigator will record any AE on the Adverse Events CRF for which the concomitant medication was administered.

9.3. Prohibited Therapies

Since ecopipam and its metabolite (SCH40853) may inhibit CYP2D6, OATP1B1, PGP and UGT1A9, for any drug that is a substrate of these enzymes, the label for the drug should be consulted to decide if a dose adjustment is needed. Drugs that are strong inducers of these enzymes are prohibited. An illustrative list of such drugs is provided in the Prohibited Medications List in the Appendices.

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

- Previous treatment with ecopipam
- Any investigational medication within 1 month prior to Screening
- Depot neuroleptics within 3 months prior to Screening
- Oral neuroleptics within 4 weeks prior to Screening

- Current use of anti-depressant, anti-anxiety or anti-ADHD medications unless the dosage has been stable for a minimum of 4 weeks prior to Screening and are not prescribed to relieve the neurological symptoms related to TS
- 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
- Initiation or changes in behavioral therapies for TS during the course of the study (i.e., Habit Reversal Training or Comprehensive Behavioral Intervention for Tics) as well as deep brain stimulation
- New behavior therapies to treat TS that were initiated fewer than 10 weeks prior to the Baseline visit

9.4. Treatment Compliance

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

9.5. Randomization and Blinding

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

A master list of all treatments and the subject numbers associated with them will be maintained electronically by the unblinded clinical supply vendor and the unblinded personnel at the CRO. The process to request a randomization code will be outlined in a separate document. The site will be trained in this process and should only be used in an emergency. These codes should only be broken only if knowledge of the subject's randomization code will affect his/her medical treatment. If necessary, the Investigator may consult with the sponsor before breaking the blind. The Investigator is to record the date and time of requesting the code and the reason for breaking the code.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Ecopipam tablets and matching placebo tablets.

10.2. Study Drug Packaging and Labeling

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

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

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

10.3. Study Drug Storage

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

10.4. Study Drug Preparation

Study drug will be prepared in 15-count bottles for ecopipam and matching placebo.

10.5. Administration

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

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

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

During the 8-week treatment phase, the following ecopipam HCl doses or matching placebo will be administered for each of the weight bands:

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

All doses will be administered PO once daily in the evening. 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 8-week treatment phase, subjects will titrate off therapy and receive ecopipam HCl doses or matching placebo that will be reduced by 25 mg/day until off of study drug. Signs of symptoms of withdrawal will be monitored.

10.6. Dosing Rationale

An ecopipam HCl dose of 2 mg/kg/day with titration is targeted in pediatric subjects aged ≥6 to <18 years using the dosage regimen proposed in Table 4.

Table 4: Proposed Dosing Regimen

Weight (kg)	Dose (mg) Week #1	Dose (mg) Week #2	Dose (mg) Week #3	Dose (mg) Week #4 onward
≥18 to ≤23	12.5	25 (2 × 12.5)	37.5 (3 × 12.5)	37.5 (3 × 12.5)
>23 to ≤34	12.5	25 (2 × 12.5)	37.5 (3 × 12.5)	50
>34 to ≤44	12.5	25 (2 × 12.5)	50	75
>44 to ≤68	25 (2 × 12.5)	50	75	100
>68 to ≤83	25 (2 × 12.5)	50	100	150 (2 × 75)
>83	25 (2 × 12.5)	50	100	200 (2 × 100)

This dosing regimen was chosen based on modeling and simulation with the results and important information summarized below:

- A double-blind, placebo-controlled, crossover study of 40 subjects with TS 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);
- 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, SCH40853) are adequate based on the no-observed-adverse-effects-level (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 in Study PSY302 (Table 5). 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 the proposed clinical study Protocol EBS-101-CL-001).
- 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 two-week titration which has the potential to improve tolerability.
- While studying multiple dose levels is important in a Phase 2b study, a dose titration approach (instead of fixed 3-dose parallel design study) was chosen because the PSY302 study suggested that doses lower than ~1.4 mg/kg the 25th percentile would be unlikely to have substantial efficacy. The exposure between ~1.4 mg/kg and ~2 mg/kg would have significant overlap in exposure (i.e., they would not be distinctly different doses), 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.

Table 5: Animal:Human Exposure Ratios with the Proposed Dosage Regimen of Ecopipam to 7- to 16-Year-Olds

Week	PK	Mice: Human Ratio[b,c]	Rhesus Monkey: Human Ratio[c]		Cynomolgus Monkey: Human Ratio[c]	
		30 mg/kg	3 mg/kg	12 mg/kg	3 mg/kg	12 mg/kg
Combined AUC[a] (ng*hr/mL)						
1	146	17.2x	2.1x	5.9x	2.1x	10.6x
2	289	8.7x	1.1x	3.0x	1.1x	5.3x
Full Dose	535	4.7x	0.6x	1.6x	0.6x	2.9x
Combined C_{max}[a] (ng/mL)						
1	17.1	16.9x	1.4x	3.4x	1.5x	8.7x
2	34.3	8.4x	0.7x	1.7x	0.8x	4.3x
Full Dose	62.6	4.6x[c]	0.4x	0.92x	0.4x	2.4x[c]

[a] Animal: human ratios were calculated based on combined unconjugated parent ecopipam plus active metabolite SCH40853 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}.

[c] Ratios were calculated using the predicted exposure in PSY302. These animal:human ratios did not differ in most cases for the full dose where the animal:human C_{max} ratios differed by 0.1× where noted.

10.7. Study Drug Accountability

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

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

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

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

Due to the COVID-19 pandemic, in some cases direct to patient shipments may be necessary. In this case, study medication may be transported to the subject by a third party vendor who has systems in place to protect blinding, patient privacy, and data integrity.

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

10.8. Study Drug Handling and Disposal

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

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

11. ASSESSMENT OF EFFICACY

Assessments may be completed in locations other than study clinic and/or via remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event.

11.1. Primary Efficacy Assessment

YGTSS will be assessed at Screening, Baseline and at Weeks 4, 6, 8 and 12.

Change in the Yale Global Tic Severity Scale – Total Tic Score (TTS, i.e., sum of the motor and phonic tic scores) from baseline (YGTSS-TTS score from Baseline visit) to end of therapy (YGTSS-TTS score at Week 12).

The YGTSS is a clinician-completed rating scale used to quantify overall tic severity as well as specific subdomains of tic number, frequency, duration, intensity, and complexity. Each of these subdomains is scored, on a 5-point scale, separately for motor and vocal tics and then summed across both motor and vocal tics to yield a tic severity score ranging from 0 to 50. The YGTSS also provides for an overall impairment rating (0 = ‘‘none’’ to 50 = ‘‘severe’’). The YGTSS has demonstrated acceptable internal consistency, good interrater reliability, and acceptable convergent and divergent validity.

11.2. Secondary Efficacy Assessments

Key Secondary Efficacy Endpoint:

- Change in Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) from Baseline to Week 12

Other Secondary efficacy endpoints include:

- Change in Clinician Global Impression Tourette Syndrome of Improvement (CGI-TS-I) from Week 4 to Week 12
- Change in YGTSS-Global Score (GS) from Baseline to Week 12
- Change in Caregiver Global Impression of Change (CaGI-C) from Week 4 to Week 12
- Change in Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) from Baseline to Week12
- Percentage of subjects with a 25% improvement on the YGTSS-TTS
- Percentage of subjects with complete remission of tics on the YGTSS-TTS
- Change in YGTSS-TTS from Baseline to Weeks 4, 6, and 8
- Change in CGI-TS-S from Baseline to Weeks 4, 6, and 8
- Change in CGI-TS-I from Baseline to Weeks 4, 6, and 8
- Change in YGTSS-GS from Baseline to Weeks 4, 6, and 8
- Change in CaGI-C from Baseline to Weeks 4, 6, and 8

- Change in the C&A-GTS-QOL from Baseline to Weeks 4, 6, and 8

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

The CGI consists of two reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms. The improvement scale will be used at every visit after the Screening and Baseline Visits. The scale ranges from 1 = "very much improved" to 7 = very much worse." The CGI severity scale will be used at each study site visit and ranges from 1 = "not ill at all" to 7 = "among the most extremely ill."

Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) is a patient-reported health related quality of life measure developed for children and adolescents.

11.3. Pharmacokinetics Parameters

Blood samples will be collected to measure concentrations of ecopipam and/or its major (active) metabolites at Weeks 4 and 12.

For the Week 4 visit, a morning appointment is suggested. Parents/caregivers will be instructed not to administer the study medication to the subject on the evening prior to the Week 4 visit and to record the time of administration of the last dose of study medication taken. The study drug administration will occur at the site on the day of the Week 4 visit under the supervision of the study investigator. An intravenous catheter will be placed, and the subject will have samples collected at the following time windows: one sample at pre-dose (34 to 44 hours since the last dose), one sample between 0.5 and 1.5 hour after administration of study medication, and one sample between 2 and 4 hours after study drug administration. Any samples should be collected at least 30 min apart.

For the Week 12 visit, parents/caregivers will be asked to record the time of study drug administration on the evening prior to the visit. An appointment is suggested to be made for the morning of the Week 12 visit. A blood sample will be collected at the end of the visit. The time of sample collection will be recorded. Blood samples will be processed as outlined in the protocol and serum/plasma will be frozen, shipped and analyzed for ecopipam and SCH40853.

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

12. ASSESSMENT OF SAFETY

Assessments may be completed in locations other than study clinic and/or via remote administration due to restrictions as a consequence of the COVID-19 pandemic or other qualifying event.

12.1. Safety Parameters

Safety will be assessed by monitoring and recording all adverse events (AEs) and SAEs (all visits), regular monitoring of hematology, blood chemistry and urine values (Screening, Baseline, Weeks 12, 7 and 14 day Follow-up visits). HbA1c will be measured at the baseline and completion/early termination visits. Regular measurement of vital signs, physical examination and an ECG (Screening, Baseline, Weeks 4, 6, 8, 12, 7 and 14 day Follow Up visit) will be performed.

12.1.1. Columbia Suicide Severity Rating Scale

An additional assessment will include the Columbia-Suicide Severity Rating Scale (C-SSRS) (all Visits except the 30-day Follow-up visit).

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

12.1.2. Other Safety Outcome Scales

Additional safety outcomes (Baseline and Weeks 4, 6, 8 and 12) will include the following:

Abnormal Involuntary Movement Scale (AIMS) records the occurrences of tardive dyskinesia (TD) in subjects receiving neuroleptic medications. The test is used to detect TD and to follow the severity over time.

Barnes Akathisia Rating Scale (BARS) scale to assess the severity of drug-induced akathisia. Objective and subjective items in the scale measure the level of subject's restlessness.

Swanson, Nolan and Pelham (SNAP-IV) questionnaire measure designed assess ADHD and oppositional defiant disorder (ODD) symptoms in children and adolescents.

Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) is a reliable and valid scale to both determine severity of OCD and to monitor improvement during treatment. The scale is a clinician-rated, 10-item scale that includes questions about the amount of spent on obsessions/compulsions, level of impairment or distress, and how much resistance and control subjects have over these thoughts.

Children's Depression Rating Scale-Revised (CDRS-R) is a clinically validated rating scale designed to assess psychiatric signs and symptoms of depressions.

Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) is a subject-reported health related quality of life measure developed for children and adolescents.

Pediatric Anxiety Rating Scale (PARS) is a clinician-rated instrument for assessing the severity of anxiety symptoms associated with common anxiety disorders and generalized anxiety in children and adolescents.

12.1.3. Other Safety Assessments

Vital signs will be collected at each clinic visit (Screening, Baseline, Weeks 4, 6, 8, 12, 7 and 14 day Follow Up visits). It includes blood pressure, orthostatic blood pressure (after being supine for 5 minutes and 3 minutes after standing) pulse, height and weight.

Clinical Laboratory Assessments:

During the following clinic visit (Screening, Baseline, Week 12, 7-day and 14 day Follow Up visits), the following clinical laboratory tests will be performed. HbA1c will be measured at the baseline and completion/early termination visits.

Clinical Laboratory Tests

Category	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelets, and white blood cell count with differential (neutrophils, bands lymphocytes, monocytes, eosinophils, basophils)
Chemistry	
Electrolytes	Sodium, potassium, chloride, bicarbonate
Liver function tests	Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin
Renal function parameters	Blood urea/blood urea nitrogen (BUN), creatinine
Other	Glucose, calcium, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, globulin
Pregnancy Test	Urine test (for women of childbearing potential only)
Special Parameters	Hemoglobin A1c (HbA1c)

Contraception Guidelines:

As specified in the Inclusion Criteria (Section 8.1), adolescent females of childbearing potential who are sexually active and male subjects who are sexually active must use a highly effective form of contraception throughout the study and for 30 days after the last dose of study drug. See the Contraception Guidelines for additional information.

Subjects must be monitored for signs of study drug abuse, and withdrawal or dependence and if detected must be recorded as AEs.

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 medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

12.2.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition including worsening of TS 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.

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. 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. Adverse events of special interest (AESI) include weight gain and extra-pyramidal reactions.

12.3. Relationship to Study Drug

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

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

12.4. Recording Adverse Events

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

Should a pregnancy of a subject or partner occur, it must be reported and recorded on Sponsor's or 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 Syneos Health Safety & Pharmacovigilance within one business day:

Email Address: SafetyPV@syneoshealth.com
Fax no. Americas: +1 866 856 1649
Fax no. Europe and ROW +44 1628 461184

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

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

12.5. Reporting 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 to Syneos Health Safety & Pharmacovigilance within 1 business day of the first awareness of the event:

Email Address: SafetyPV@syneoshealth.com
Fax no. Americas: +1 866 856 1649
Fax no. Europe and ROW +44 1628 461184

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

Additional follow-up information, if required or available, should all be sent to the Sponsor or its representatives within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

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

13. STATISTICS

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

13.1. Analysis Population

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

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. Protocol deviations that occur due to COVID-19 related issues will be categorized separately as applicable.

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

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

13.2. Planned Analysis

13.2.1. Efficacy Analysis

The primary efficacy endpoint for this study will be the change from Baseline (score of YGTSS-TTS at Baseline) to end of therapy (score of YGTSS-TTS at Week 12). The analysis of primary efficacy endpoint will be performed in mITT and PP populations according to the randomized treatment.

The primary endpoint will be assessed with a Mixed Model for Repeated Measures (MMRM) model 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 YGTSS-TTS score. If the sample size has been increased as a result of the interim analysis, the CHW (Cui-Hung-Wang) method will be used to control the type 1 error in the MMRM model. Taking consideration of missing data, multiple imputation or tipping point method may be used as a sensitivity analysis.

YGTSS-Global Score (YGTSS-GS), Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S), Clinical Global Impression of Tourette Syndrome Improvement (CGI-TS-I),

Caregiver Clinical Global Impression of Change (CaGI-C) and C&A-GTS-QOL will be analyzed using MMRM if appropriate. The treatment difference at Week 4, 8 and 12 can be estimated based on MMRM.

The percentage of subjects with a 25% improvement on the YGTSS-TS can be analyzed using Fisher Exact test.

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 rank order hierarchy which will be outlined in the SAP.

The full details and any sensitivity analyses will be specified in the SAP.

13.2.2. Safety Analysis

All safety data will be summarized in Safety population according to the actual treatment.

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

The Columbia-Suicide Severity Rating Scale (C-SSRS), Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale, the Swanson, Nolan and Pelham (SNAP-IV) questionnaire, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), the Children's Depression Rating Scale-Revised (CDRS-R) and the Pediatric Anxiety Rating Scale (PARS) 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 the pharmacokinetics population.

13.2.4. Data Safety Monitoring Board

An independent data safety and monitoring board (DSMB) consisting of a physician experienced in the conduct of clinical studies (Chairman with TS experience), one clinician and one statistician experienced in TS will review the data at the interim analysis. The data will be cleaned by the data management group, and the analysis and reporting of the interim data to the DSMB will be the responsibility of an independent statistical group (who will not be directly involved in the conduct of the study). The DSMB will meet after the data presentation and issue recommendations relating to safety and study conduct; after the interim analysis, these recommendations may also include stopping the study for futility or increasing the sample size. The rationale for these recommendations will be documented in a set of minutes as to the safety and viability (i.e., conditional power) of the study to reach its goals at study completion. The

minutes of the DSMB will be submitted to the sponsor after the study has been unblinded and will be appended to the final study report.

13.2.5. Interim Analysis

Interim analyses will be completed in coordination with the Data Safety Monitoring Board (DSMB) meetings to primarily assess safety and preliminary efficacy. An interim analysis will be conducted after approximately 50% of subjects have enrolled and completed treatment or early termination procedures are completed. These interim analyses will be performed by an independent statistician and governed by an external DSMB. The DSMB will assess the safety data as well as the probability of a successful study based on observed data (conditional power). The DSMB could recommend stopping the study for futility. The decision to stop the study will include evaluating the probability of successful study (conditional power), as well as safety data and other prespecified criteria to be described in the DSMB charter. The DSMB can also recommend the continuation of the study as planned or with a sample size adjustment based on the conditional power. If the sample size is adjusted, the CHW (Cui-Hung-Wang) method will be used to control the type 1 error in the final analysis.

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

13.3. Sample Size Justifications

A sample size of 75 subjects per group will provide >80% power to detect difference between groups of 3 points on change from baseline the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS), with standard deviation = 6.1 and alpha = 0.05, assuming 10% drop out.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

14.1. Study Monitoring

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

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities 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 sent to Emalex.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor or its representatives and those SAEs that met criteria for reporting have been forwarded to the IRB.

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

14.2. Audits and Inspections

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

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

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

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

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (please see Appendix <insert #>) and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the Sponsor's policy on Bioethics.

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.

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

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

16.4. Subject Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is strictly prohibited. Upon the subject's

permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her medical welfare.

The Sponsor will use the information obtained during the conduct of this study for the development of ecopipam. The study Investigator is obliged to provide the Sponsor with complete test results and all data developed in this study, 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 study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

17.2. Retention of Records

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

18. PUBLICATION POLICY

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

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

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

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

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21. APPENDICES

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

Preamble

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

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

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

General Principles

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

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

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

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

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

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

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must

always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

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

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

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

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

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

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

Risks, Burdens and Benefits

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

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

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

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

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

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

Vulnerable Groups and Individuals

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

All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

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

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

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

Research Ethics Committees

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

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the

committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

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

Informed Consent

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

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

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

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

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

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

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that

assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

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

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

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

Use of Placebo

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

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

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

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

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

Post-Trial Provisions

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

Research Registration and Publication and Dissemination of Results

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

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

Unproven Interventions in Clinical Practice

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

CONTRACEPTION GUIDELINES

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

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

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

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

PROHIBITED MEDICATIONS LIST

Examples below are not exclusive.

- Any new stimulant for the treatment of ADHD that the subject was not taking at randomization is also prohibited.
- Other medications used to treat TS are prohibited.
- Dopamine depleting medications are prohibited.
- D2 receptor antagonists prohibited.

Prohibited Antipsychotic Medications	
Aripiprazole	Loxapine
Cisapride	Methylphenidate
Clonidine	Paliperidone
Dextroamphetamine	Pimozide
Dronedarone	Risperidone
Droperidol	Thioridazine
Fluoxetine	Topiramate
Guanfacine	Ziprasidone
Haloperidol	

Other Prohibited Medications for the Treatment of Tics	**Mechanism**
Any dopamine agonist (e.g., ropinirole, pramipexole)	
Baclofen	GABA-B receptor agonist
Clonazepam	GABA-A receptor positive allosteric modulation
Duetetrabenazine	VMAT2 inhibitor / monoamine depleter
Guanfacine	Alpha-2A adrenergic receptor agonist
Reserpine	VMAT1/2 inhibitor / inhibits uptake of dopamine
Tetrabenazine	VMAT2 inhibitor / monoamine depleter
Valbenazine	VMAT2 inhibitor / monoamine depleter

Other Prohibited Medications	Mechanism
Chloroethylnorapomorphine	D2 receptor antagonist
Chlorpromazine	D2 receptor antagonist/ antipsychotic
Cinnarizine	Antihistamine/ calcium channel blocker/ Interaction with D2 receptors
Desmethoxyfallypride	D2/D3 receptor antagonist used as PET radiotracer
Domperidone	D2/D3 receptor antagonist/ antiemetic
Eticlopride	D2 receptor antagonist
Fallypride	D2/D3 receptor antagonist used as PET radiotracer
Hydroxyzine	H1 receptor antagonist
Itopride	D2 receptor antagonist/used as treatment for GI disorders
Metclopramide	D2 receptor antagonist/ antiemetic

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

The dose of Sensitive CYP2D6 substrates that may need to be reduced (according to their respective labels)	
Atomoxetine	Sensitive CYP2D6 substrate
Codeine	Sensitive CYP2D6 substrate
Desipramine	Sensitive CYP2D6 substrate
Dextromethorphan	Sensitive CYP2D6 substrate
Deutetrabenazine	Sensitive CYP2D6 substrate
Doxepin	Sensitive CYP2D6 substrate
Eliglustat	Sensitive CYP2D6 substrate
Encainide	Sensitive CYP2D6 substrate
Enclomiphene	Sensitive CYP2D6 substrate
Ibogaine	Sensitive CYP2D6 substrate
Metoprolol	Sensitive CYP2D6 substrate
Methoxyphenamine	Sensitive CYP2D6 substrate
Nebivolol	Sensitive CYP2D6 substrate
Nicergoline	Sensitive CYP2D6 substrate
Paroxetine	Sensitive CYP2D6 substrate
Perhexiline	Sensitive CYP2D6 substrate
Perphenazine	Sensitive CYP2D6 substrate
Prajmaline	Sensitive CYP2D6 substrate
Propafenone	Sensitive CYP2D6 substrate
Repinotan (IV)	Sensitive CYP2D6 substrate
Risperidone	Sensitive CYP2D6 substrate
Tamoxifen	Sensitive CYP2D6 substrate
Tolperisone	Sensitive CYP2D6 substrate
Tolterodine	Sensitive CYP2D6 substrate
Tramadol	Sensitive CYP2D6 substrate
Traxoprodil	Sensitive CYP2D6 substrate
Trimipramine	Sensitive CYP2D6 substrate
Tropisetron	Sensitive CYP2D6 substrate
Venlafaxine	Sensitive CYP2D6 substrate
Vernakalant	Sensitive CYP2D6 substrate

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

PGP substrates: dose of these PGP substrates should be adjusted based on their respective labels	
Acalabrutinib	PGP substrates
Adafosbuvir (AL-335)	PGP substrates
Albendazole	PGP substrates
Aliskiren	PGP substrates
Alisporivir	PGP substrates
Ambrisentan	PGP substrates
Amd070	PGP substrates
Amenamevir	PGP substrates
Apixaban	PGP substrates
Asunaprevir	PGP substrates
Atecegatran metoxil	PGP substrates
Atorvastatin (acid)	PGP substrates
Avatrombopag	PGP substrates
Azithromycin	PGP substrates
Betrixaban	PGP substrates

PGP substrates: dose of these PGP substrates should be adjusted based on their respective labels	
Bictegravir	PGP substrates
Buprenorphine	PGP substrates
Celiprolol	PGP substrates
Cerivastatin (acid)	PGP substrates
Colchicine	PGP substrates
Copanlisib	PGP substrates
Cp-481,715	PGP substrates
Cyclosporine	PGP substrates
Dabigatran	PGP substrates
Danoprevir	PGP substrates
Deflazacort	PGP substrates
Dicloxacillin	PGP substrates
Digoxin	PGP substrates
Docetaxel	PGP substrates
Domperidone	PGP substrates
Doravirine	PGP substrates
Doxorubicin	PGP substrates
Edoxaban	PGP substrates
Elbasvir	PGP substrates
Emtricitabine	PGP substrates
Erlotinib	PGP substrates
Erythromycin	PGP substrates
Etoposide	PGP substrates
Everolimus	PGP substrates
Fentanyl	PGP substrates
Fexofenadine	PGP substrates
Glecaprevir	PGP substrates
Idarubicin	PGP substrates
Indinavir	PGP substrates
Irinotecan	PGP substrates
Itraconazole	PGP substrates

PGP substrates: dose of these PGP substrates should be adjusted based on their respective labels	
Ivosidenib	PGP substrates
Lapatinib	PGP substrates
Larotrectinib	PGP substrates
Ledipasvir	PGP substrates
Letermovir	PGP substrates
Linezolid	PGP substrates
Loperamide	PGP substrates
Losartan	PGP substrates
Maraviroc	PGP substrates
Maraviroc	PGP substrates
Mirabegron	PGP substrates
Mitoxantrone	PGP substrates
Morphine	PGP substrates
Nadolol	PGP substrates
Naldemedine	PGP substrates
Naloxegol	PGP substrates
Nevirapine	PGP substrates
Nintedanib	PGP substrates
Octreotide	PGP substrates
Olodaterol	PGP substrates
Paclitaxel	PGP substrates
Paritaprevir	PGP substrates
Paroxetine	PGP substrates
Pazopanib	PGP substrates
Phenytoin	PGP substrates
Pibrentasvir	PGP substrates
Pravastatin (acid)	PGP substrates
Proguanil	PGP substrates
Quetiapine	PGP substrates
Quinidine	PGP substrates
Ranitidine	PGP substrates

PGP substrates: dose of these PGP substrates should be adjusted based on their respective labels	
Ranolazine	PGP substrates
Rivaroxaban	PGP substrates
Rosuvastatin (acid)	PGP substrates
Saquinavir	PGP substrates
Selexipag	PGP substrates
Simeprevir	PGP substrates
Simvastatin (lactone)	PGP substrates
Sirolimus	PGP substrates
Sofosbuvir	PGP substrates
Sotrastaurin	PGP substrates
Tacrolimus	PGP substrates
Talinolol	PGP substrates
Tedisamil	PGP substrates
Teneligliptin	PGP substrates
Tenofovir	PGP substrates
Ticagrelor	PGP substrates
Velpatasvir	PGP substrates
Venetoclax	PGP substrates
Venlafaxine	PGP substrates
Verapamil	PGP substrates
Vinblastine	PGP substrates
Vincristine	PGP substrates
Voclosporin	PGP substrates
Ximelagatran	PGP substrates

UGT1A1 substrates: dose of these UGT1A1 substrates should be adjusted based on their respective labels	
Clopidogrel	UGT1A9 substrate
Furosemide	UGT1A9 substrate
Mycophenolic acid	UGT1A9 substrate
Probenecid	UGT1A9 substrate
Propofol	UGT1A9 substrate