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

Summary

EudraCT number	2019-000282-20
Trial protocol	FR PL
Global end of trial date	11 November 2022

Results information

Result version number	v1 (current)
This version publication date	26 November 2023
First version publication date	26 November 2023

Trial information

Trial identification

Sponsor protocol code	EBS-101-OL-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04114539
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Emalex Biosciences, Inc.
Sponsor organisation address	330 North Wabash Avenue, Suite 3500, Chicago, United States, 60611
Public contact	Sr. Director of Clinical Operations, Emalex Biosciences, Inc. , +1 8477150562, dkim@emalexbiosciences.com
Scientific contact	Sr. Director of Clinical Operations, Emalex Biosciences, Inc. , +1 8477150562, dkim@emalexbiosciences.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the long-term safety and tolerability of ecopipam tablets in pediatric subjects (aged greater than or equal to (>=) 6 to less than or equal to (<=) 18 years at Baseline) with Tourette's Syndrome (TS) that were previously enrolled in the EBS-101-CL-001 study within the time period specified in the protocol.

Protection of trial subjects:

The study was conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations in compliance with International Council for Harmonisation (ICH) good clinical practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	United States: 91
Worldwide total number of subjects	121
EEA total number of subjects	24

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	39
Adolescents (12-17 years)	80
Adults (18-64 years)	2

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 39 sites in United States, Canada and Poland from 4 October 2019 (first subject first visit) to 11 November 2022 (last subject last visit).

Pre-assignment

Screening details:

A total of 124 subjects who completed the open-labelled study EBS-101-CL-001 (NCT04007991) and who met the inclusion/exclusion criteria for this study were enrolled in the current study and received study treatment. Of the 124 enrolled subjects, 121 subjects were included in the modified ITT (mITT) Set and Safety Set.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ecopipam HCI 2 mg/kg/Day

Arm description:

Subjects received ecopipam hydrochloride (HCl) tablets at a targeted dose of 2 milligram per kilogram per day (mg/kg/day), orally, once daily for up to 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Ecopipam HCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Ecopipam HCl tablets at a targeted dose of 2 mg/kg/day, orally, once daily.

Number of subjects in period 1	Ecopipam HCI 2 mg/kg/Day
Started	121
Completed	80
Not completed	41
Non-compliance with Study Drug	1
Withdrawal by Parent/Caregiver	8
Adverse event, non-fatal	14
Not specified	2
Non-compliance with protocol	2
Investigator Decision	2
Lost to follow-up	2
Withdrew consent	10

Baseline characteristics

Reporting groups	
Reporting group title	Ecopipam HCI 2 mg/kg/Day
Reporting group description:	
Subjects received ecopipam hydrochloride (HCl) tablets at a targeted dose of 2 milligram per kilogram per day (mg/kg/day), orally, once daily for up to 52 weeks.	

Reporting group values	Ecopipam HCI 2 mg/kg/Day	Total	
Number of subjects	121	121	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	39	39	
Adolescents (12-17 years)	80	80	
Adults (18-64 years)	2	2	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	12.8		
standard deviation	± 2.82	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	89	89	
Ethnicity Units: Subjects			
Hispanic or Latino	14	14	
Not Hispanic or Latino	107	107	
Race Units: Subjects			
Asian	3	3	
Black or African American	7	7	
White	110	110	
Unknown or Not Reported	1	1	

End points

End points reporting groups

Reporting group title	Ecopipam HCI 2 mg/kg/Day

Reporting group description:

Subjects received ecopipam hydrochloride (HCl) tablets at a targeted dose of 2 milligram per kilogram per day (mg/kg/day), orally, once daily for up to 52 weeks.

Primary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs) and Their Relationship (Unrelated, Possibly Related, or Probably Related)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs) and Their Relationship (Unrelated, Possibly Related, or Probably Related)[1]

End point description:

An AE was any untoward medical condition that occurs in a subject while participating in this clinical study. It can 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. An SAE was any untoward medical occurrence that at any dose met one, more of the following criteria: results in death, life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent, significant disability/incapacity, a congenital abnormality/birth defect, an important medical event. The relationship of the study drug in causing or contributing to the AE whether unrelated, possibly related, or probably related was decided by investigator medical judgment. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study.

End point type	Primary

End point timeframe:

From start of study drug administration until 30 days after last dose (Up to Month 13)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCI 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	121			
Units: subjects				
Subjects with any AEs	84			
Subjects with any SAEs	2			
Subjects with unrelated AEs	44			
Subjects with possibly related AEs	27			
Subjects with probably related AEs	13			
Subjects with unrelated SAEs	1			
Subjects with possibly related SAEs	1			
Subjects with probably related SAEs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hematology Parameters: Basophils to Leukocytes Ratio Reported in Percentage of Cells

End point title	Change From Baseline in Hematology Parameters: Basophils to Leukocytes Ratio Reported in Percentage of Cells[2]

End point description:

Basophils/Leukocytes was measured in percentages (%). Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in basophils to leukocytes ratio is reported in terms of percentage of cells. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percentage of cells				
arithmetic mean (standard deviation)	-0.1 (± 0.91)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hematology Parameters: Eosinophils to Leukocytes Ratio Reported in Percentage of Cells

End point title	Change From Baseline in Hematology Parameters: Eosinophils to Leukocytes Ratio Reported in Percentage of Cells[3]

End point description:

Eosinophils/Leukocytes was measured in percentages (%). Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in eosinophils to leukocytes ratio is reported in terms of percentage of cells. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCI 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percentage of cells				
arithmetic mean (standard deviation)	0.1 (± 1.52)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hematology Parameters: Erythrocytes

End point title	Change From Baseline in Hematology Parameters:

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in hematology parameter erythrocytes was reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCI 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: 10^12 cells per liter				
arithmetic mean (standard deviation)	0.04 (± 0.263)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hematology Parameters: Hematocrit

End point title	Change From Baseline in Hematology Parameters:

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in hematology parameter hematocrit was reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: liter of cells per liter of blood (L/L)				
arithmetic mean (standard deviation)	0.01 (± 0.029)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hematology Parameters: Hemoglobin

End point title	Change From Baseline in Hematology Parameters:

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in hematology parameter hemoglobin was reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: millimoles per liter (mmoL/L)				
arithmetic mean (standard deviation)	0.08 (± 0.429)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hematology Parameters: Leukocytes and Platelets

End point title	Change From Baseline in Hematology Parameters: Leukocytes and Platelets[7]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in hematology parameters (Leukocytes and Platelets) expressed in 10^9 cells per liter were reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: 10^9 cells per liter				
arithmetic mean (standard deviation)				
Leukocytes	0.15 (± 1.349)			
Platelets	4.1 (± 51.49)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hematology Parameters: Lymphocytes to Leukocytes Ratio Reported in Percentage of Cells

End point title	Change From Baseline in Hematology Parameters: Lymphocytes to Leukocytes Ratio Reported in Percentage of Cells[8]

End point description:

Lymphocytes/leukocytes was measured in percentages (%). Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in lymphocytes to leukocytes ratio is reported in terms of percentage of cells. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percentage of cells				
arithmetic mean (standard deviation)	0.2 (± 10.20)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hematology Parameters: Monocytes to Leukocytes Ratio Reported in Percentage of Cells

End point title	Change From Baseline in Hematology Parameters: Monocytes to Leukocytes Ratio Reported in Percentage of Cells[9]

End point description:

Monocytes/leukocytes was measured in percentages (%). Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in monocytes to leukocytes ratio is reported in terms of percentage of cells. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percentage of cells				
arithmetic mean (standard deviation)	0.2 (± 1.43)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hematology Parameters: Neutrophils to Leukocytes Ratio Reported in Percentage of Cells

End point title	Change From Baseline in Hematology Parameters: Neutrophils to Leukocytes Ratio Reported in Percentage of Cells[10]

End point description:

Neutrophils/leukocytes was measured in percentages (%). Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in neutrophils to leukocytes ratio is reported in terms of percentage of cells. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percentage of cells				
arithmetic mean (standard deviation)	-0.3 (± 10.45)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Serum Chemistry Parameters: Alanine Aminotransferase, Alkaline Phosphatase, Aspartate Aminotransferase, Lactase Dehydrogenase

End point title	Change From Baseline in Serum Chemistry Parameters: Alanine Aminotransferase, Alkaline Phosphatase, Aspartate Aminotransferase, Lactase Dehydrogenase[11]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in Serum chemistry parameters (alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transferase, and lactate dehydrogenase) expressed in units per liter (U/L) were reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and "n" signifies subjects who were evaluable for specific categories.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: units per liter (U/L)				
arithmetic mean (standard deviation)				
Alanine Aminotransferase (n=29)	2.3 (± 9.41)			
Alkaline Phosphatase (n=29)	-4.7 (± 80.71)			
Aspartate Aminotransferase (n=29)	-0.3 (± 5.48)			
Lactase Dehydrogenase (n=26)	-6.2 (± 33.96)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Serum Chemistry Parameters: Albumin, Globulin and Protein

End point title	Change From Baseline in Serum Chemistry Parameters: Albumin, Globulin and Protein[12]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in Serum chemistry parameters (albumin, globulin and protein) expressed in grams per liter (g/L) were reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)				
Albumin	0.6 (± 2.87)			
Globulin	1.2 (± 2.92)			
Protein	1.9 (± 4.63)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Serum Chemistry Parameters: Bicarbonate, Calcium, Chloride, Cholesterol, Glucose, Phosphate, Potassium, Sodium, Triglyceride and Urea Nitrogen

End point title	Change From Baseline in Serum Chemistry Parameters: Bicarbonate, Calcium, Chloride, Cholesterol, Glucose, Phosphate, Potassium, Sodium, Triglyceride and Urea Nitrogen[13]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in Serum chemistry parameters (bicarbonate, calcium, chloride, cholesterol, glucose, phosphate, potassium, sodium, triglyceride, urea nitrogen) expressed in millimoles per liter (mmol/L) were reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Bicarbonate	-0.6 (± 3.57)			
Calcium	0.02 (± 0.153)			
Chloride	-0.2 (± 2.54)			
Cholesterol	0.20 (± 0.704)			
Glucose	-0.06 (± 0.781)			
Phosphate	-0.02 (± 0.294)			
Potassium	0.02 (± 0.684)			
Sodium	-0.1 (± 2.22)			
Triglyceride	-0.09 (± 0.625)			
Urea Nitrogen	-0.07 (± 1.176)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Serum Chemistry Parameters: Bilirubin, Creatinine and Direct Bilirubin

End point title	Change From Baseline in Serum Chemistry Parameters: Bilirubin, Creatinine and Direct Bilirubin[14]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in Serum chemistry parameters (bilirubin, creatinine and direct bilirubin) expressed in micromole per liter (mcmol/L) were reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and n signifies subjects who were evaluable for specific categories.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: micromole per liter (mcmol/L)				
arithmetic mean (standard deviation)				
Bilirubin (n=26)	-0.6 (± 4.78)			
Creatinine (n=29)	6.2 (± 8.85)			
Direct Bilirubin (n=28)	-0.1 (± 0.77)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hemoglobin A1c (HbA1c)

End point title	Change From Baseline in Hemoglobin A1c (HbA1c)[15]

End point description:

HbA1c is the glycosylated fraction of hemoglobin A. It is measured to identify average blood glucose concentration over prolonged periods of time. Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in HbA1c was reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	0.03 (± 0.313)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Vital Signs Parameter: Diastolic Blood Pressure and Systolic Blood Pressure

End point title	Change From Baseline in Vital Signs Parameter: Diastolic Blood Pressure and Systolic Blood Pressure[16]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in vital signs parameters diastolic blood pressure and systolic blood pressure and according to the assessment position (supine and standing) expressed in

millimeter(s) of mercury (mmHg) was reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and "n" signifies subjects who were evaluable at specific categories.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: mmHg				
arithmetic mean (standard deviation)				
Diastolic Blood Pressure (n=74)	0.9 (± 9.96)			
Diastolic Blood Pressure: Supine (n=74)	0.6 (± 8.58)			
Diastolic Blood Pressure: Standing (n=75)	1.6 (± 10.65)			
Systolic Blood Pressure (n=74)	0.3 (± 11.47)			
Systolic Blood Pressure: Supine (n=74)	1.8 (± 11.35)			
Systolic Blood Pressure: Standing (n=75)	-1.1 (± 12.15)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Vital Signs Parameter: Pulse Rate

End point title	Change From Baseline in Vital Signs Parameter: Pulse Rate[17]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in vital sign parameter pulse rate and according to assessment position (supine and standing) was reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and "n"signifies subjects who were evaluable at specific categories.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Pulse Rate (n=74)	0.4 (± 13.76)			
Pulse Rate Supine (n=74)	0.6 (± 14.20)			
Pulse Rate Standing (n=75)	1.8 (± 18.09)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Vital Signs Parameter: Body Mass Index [BMI]

End point title	Change From Baseline in Vital Signs Parameter: Body Mass Index [BMI][18]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in vital signs parameter BMI was reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: kilograms per square meter (kg/m^2)				
arithmetic mean (standard deviation)	1.0 (± 4.58)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Vital Signs Parameter: Height

End point title	Change From Baseline in Vital Signs Parameter: Height[19]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in vital signs height was reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: centimeter (cm)				
arithmetic mean (standard deviation)	4.0 (± 3.90)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Vital Signs Parameter: Weight

End point title	Change From Baseline in Vital Signs Parameter: Weight[20]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change from baseline in vital signs parameter weight was reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline to Month 12

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: kilogram (kg)				
arithmetic mean (standard deviation)	5.4 (± 13.53)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Electrocardiogram (ECG) Values Parameters: Aggregate PR Interval, Aggregate QRS Duration, Aggregate QT Interval, and Aggregate QTc Interval

End point title	Change From Baseline in Electrocardiogram (ECG) Values Parameters: Aggregate PR Interval, Aggregate QRS Duration, Aggregate QT Interval, and Aggregate QTc Interval[21]

End point description:

Baseline was defined as the last measurement taken before the first dose of open-label treatment on Day 1 of current study. Change From Baseline in ECG parameters aggregate PR interval, aggregate QRS duration, aggregate QT interval, and aggregate QTc interval expressed in millisecond (msec) was reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: millisecond (msec)				
arithmetic mean (standard deviation)				
Aggregate PR interval	-5.6 (± 18.81)			
Aggregate QRS duration	-0.6 (± 9.76)			
Aggregate QT interval	5.5 (± 30.26)			
Aggregate QTc interval	0.2 (± 38.53)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Abnormal Physical Examination Findings

End point title	Number of Subjects With Clinically Significant Abnormal Physical Examination Findings[22]

End point description:

Physical examination included examination of the following body areas and systems: Head, Eyes, Ears, Nose, Mouth, Throat, Neck (including Thyroid), Thorax, Abdomen, Urogenital, Extremities, Neurological, Skin and Mucosae and Others. Any clinically significant abnormalities in physical examination were judged by the investigator. Only non-zero values are reported. The Safety Set included all subjects who received at least one dose of study drug from the open labelled study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and "n" signifies subjects who were evaluable at specific categories.

End point type	Primary

End point timeframe:

Baseline up to Month 12

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Subjects				
Neurological (n=74)	1			
Other (n=1)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Yale Global Tic Severity Scale -Total Tic Score (YGTSS-TTS) at Months 1, 3, 6, 9 and 12

End point title	Change From Baseline in the Yale Global Tic Severity Scale - Total Tic Score (YGTSS-TTS) at Months 1, 3, 6, 9 and 12

End point description:

The YGTSS was a clinician-completed rating scale used to quantify overall tic severity as well as specific subdomains of tic number, frequency, intensity, complexity and interference. Each of these subdomains was scored, on a 0 to 5 scale, separately for motor and vocal tics and then summed across both motor and vocal tics to yield a total tic score ranging from 0 to 50. Higher scores represent more severe symptoms. A negative change from baseline indicates improvement. The mITT set included all subjects who received at least one dose of study drug and had at least one post Baseline scoring of YGTSS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n" signifies subjects who were evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline up to Months 1, 3, 6, 9 and 12

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Change at Month 1 (n=119)	-6.5 (± 7.10)			
Change at Month 3 (n=114)	-7.5 (± 8.04)			
Change at Month 6 (n=99)	-10.6 (± 8.88)			
Change at Month 9 (n=91)	-11.5 (± 8.34)			
Change at Month 12 (n=81)	-11.7 (± 9.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Yale Global Tic Severity Scale - Impairment (YGTSS-I) at Months 1, 3, 6, 9 and 12

End point title	Change From Baseline in the Yale Global Tic Severity Scale - Impairment (YGTSS-I) at Months 1, 3, 6, 9 and 12

End point description:

The YGTSS was 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 was scored, on 0 to 5 scale, separately for an overall impairment rating from (0 = ''none'' to 50 = ''severe''). Higher score represent more severe symptoms. A negative change from baseline indicates improvement. The mITT set included all subjects who received at least one dose of study drug and had at least one post Baseline scoring of YGTSS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n" signifies subjects who were evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline up to Months 1, 3, 6, 9 and 12

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Change at Month 1 (n=119)	-7.2 (± 9.74)			
Change at Month 3 (n=114)	-8.3 (± 10.88)			
Change at Month 6 (n=99)	-10.4 (± 10.49)			
Change at Month 9 (n=91)	-12.5 (± 11.11)			
Change at Month 12 (n=81)	-12.1 (± 11.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Yale Global Tic Severity Scale - Global Score (YGTSS-GS) at Months 1, 3, 6, 9 and 12

End point title	Change From Baseline in the Yale Global Tic Severity Scale - Global Score (YGTSS-GS) at Months 1, 3, 6, 9 and 12

End point description:

YGTSS was 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 was scored, on 0 to 5 scale, separately for motor and vocal tics and summed across both motor and vocal tics to yield a tic severity score ranging from 0 to 50. YGTSS provides overall impairment rating (0=none,50=severe). YGTSS-GS is the total of YGTSS-TTS and YGTSS-I. The maximum YGTSS Global score is 100, while maximum motor score is 25, the maximum vocal score is 25, and maximum impairment score is 50. Higher scores indicate more severe tics. A negative change from baseline indicates improvement. The mITT set included all subjects who received at least one dose of study drug and had at least 1 post Baseline scoring of YGTSS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n" signifies subjects who were evaluable at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline up to Months 1, 3, 6, 9 and 12

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Change at Month 1 (n=119)	-13.8 (± 15.07)			
Change at Month 3 (n=114)	-15.9 (± 16.91)			
Change at Month 6 (n=99)	-21.0 (± 17.64)			
Change at Month 9 (n=91)	-24.0 (± 17.31)			
Change at Month 12 (n=81)	-23.8 (± 19.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression of Tourette Syndrome of Severity (CGI-TS-S) at Months 1, 3, 6, 9, 12

End point title	Change From Baseline in Clinical Global Impression of Tourette Syndrome of Severity (CGI-TS-S) at Months 1, 3, 6, 9, 12

End point description:

The CGI consists of 2 reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms. The CGI severity scale (CGI-TS-S) ranges from 1 = "not ill at all" to 7 = "among the most extremely ill." Higher scores represent more severe symptoms. A negative change from baseline indicates improvement. The mITT set included all subjects who received at least one dose of study drug and had at least one post Baseline scoring of YGTSS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n" signifies subjects who were evaluable at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline up to Months 1, 3, 6, 9, 12

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Change at Month 1 (n=119)	-0.8 (± 1.02)			
Change at Month 3 (n=114)	-0.8 (± 1.10)			
Change at Month 6 (n=99)	-1.0 (± 1.10)			
Change at Month 9 (n=91)	-1.2 (± 1.13)			

Change at Month 12 (n=81)	-1.2 (± 1.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression Tourette Syndrome of Improvement (CGI-TS-I) Scores at Months 1, 3, 6, 9 and 12

End point title	Clinical Global Impression Tourette Syndrome of Improvement (CGI-TS-I) Scores at Months 1, 3, 6, 9 and 12

End point description:

The CGI consists of 2 reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms. The scale ranges from 1 = "very much improved" to 7 = very much worse" for the CGI-TS-I. Higher score represent more severe symptoms. The mITT set included all subjects who received at least one dose of study drug and had at least one post Baseline scoring of YGTSS. Here, "Number of subjects analyzed" signifies subjects who were evaluable for this endpoint and "n" signifies subjects who were evaluable at specified timepoints.

End point type	Secondary

End point timeframe:

Months 1, 3, 6, 9 and 12

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 1 (n=120)	2.7 (± 1.05)			
Month 3 (n=114)	2.5 (± 1.24)			
Month 6 (n=99)	2.2 (± 1.04)			
Month 9 (n=91)	2.0 (± 1.02)			
Month 12 (n=81)	2.0 (± 1.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Gilles de la Tourette Syndrome-Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) Total Score at Months 1, 3, 6, 9 and 12

End point title	Change From Baseline in Gilles de la Tourette Syndrome-Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) Total Score at Months 1, 3, 6, 9 and 12

End point description:

C&A-GTS-QOL was 27-item questionnaire specific to TS patients which assess, extent to which quality of

life is impacted by symptoms. It consists of 6 subscales (cognitive [range 0-32], psychological [range 0-24], obsessive-compulsive [range 0-16], coprophenomena, physical & activities of daily living (ADL) [range 0-12]) & uses 5 point Likert scale ranging from no problem to extreme problem. Scores for 6 subscales were generated by summing items and transforming to range of 0 to 100(100*[(observed score-min possible score)/(max possible score-min possible score)]). Total score was normalized to 0 to 100 range. Higher score=worst quality of life. A negative change from baseline=better quality of life. mITT set included all subjects who received at least 1 dose of study drug and had at least 1 post Baseline scoring of YGTSS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n" signifies subjects evaluable at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline up to Months 1, 3, 6, 9 and 12

End point values	Ecopipam HCl 2 mg/kg/Day			
Subject group type	Reporting group			
Number of subjects analysed	117			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Change at Month 1 (n=117)	-4.0 (± 11.30)			
Change at Month 3 (n=114)	-4.5 (± 12.30)			
Change at Month 6 (n=98)	-7.7 (± 13.97)			
Change at Month 9 (n=91)	-6.7 (± 16.91)			
Change at Month 12 (n=80)	-8.0 (± 16.17)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline up to 30 days after last dose of the study drug (Up to Month 13)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Ecopipam HCI 2 mg/kg/Day

Reporting group description:

Subjects received ecopipam hydrochloride (HCl) tablets at a targeted dose of 2 milligram per kilogram per day (mg/kg/day), orally, once daily for up to 52 weeks.

Serious adverse events	Ecopipam HCI 2 mg/kg/Day		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 121 (1.65%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin laceration			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Obsessive thoughts			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ecopipam HCl 2 mg/kg/Day		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 121 (69.42%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Vein collapse			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	7 / 121 (5.79%)		
occurrences (all)	9		
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Polycystic ovaries			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	3 / 121 (2.48%)		
occurrences (all)	4		
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Psychiatric disorders			
Aggression			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Agitation			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	11 / 121 (9.09%)		
occurrences (all)	12		
Attention deficit hyperactivity disorder			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Bruxism			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Compulsions			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	5 / 121 (4.13%)		
occurrences (all)	8		
Depressive symptom			

subjects affected / exposed	2 / 121 (1.65%)			
occurrences (all)	2			
Dissociative disorder				
subjects affected / exposed	2 / 121 (1.65%)			
occurrences (all)	2			
Initial insomnia				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Insomnia				
subjects affected / exposed	9 / 121 (7.44%)			
occurrences (all)	9			
Intentional self-injury				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Irritability				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Major depression				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Mental disorder				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Mood altered				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Mood swings				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Obsessive-compulsive disorder				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Panic attack				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Restlessness				

subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Social anxiety disorder			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Suicidal behaviour			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Suicidal ideation			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Terminal insomnia			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	2		
Tic			
subjects affected / exposed	5 / 121 (4.13%)		
occurrences (all)	6		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Contusion			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Fall			

subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Foot fracture			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Limb injury			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Penis injury			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Skin abrasion			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	3		
Skin laceration			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Testicular injury			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Tooth injury			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Tourette’s disorder			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	3		
Nervous system disorders			

Akathisia				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Balance disorder				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Dizziness				
subjects affected / exposed	3 / 121 (2.48%)			
occurrences (all)	3			
Formication				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Headache				
subjects affected / exposed	9 / 121 (7.44%)			
occurrences (all)	9			
Migraine				
subjects affected / exposed	2 / 121 (1.65%)			
occurrences (all)	2			
Narcolepsy				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Paraesthesia				
subjects affected / exposed	2 / 121 (1.65%)			
occurrences (all)	2			
Postural tremor				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Somnolence				
subjects affected / exposed	8 / 121 (6.61%)			
occurrences (all)	8			
Syncope				
subjects affected / exposed	3 / 121 (2.48%)			
occurrences (all)	4			
Tongue biting				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			

Tremor subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2		
Eye disorders Vision blurred subjects affected / exposed occurrences (all) Visual impairment subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1 1 / 121 (0.83%) 1		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Tooth impacted	1 / 121 (0.83%) 2 4 / 121 (3.31%) 7 5 / 121 (4.13%) 5 2 / 121 (1.65%) 2 9 / 121 (7.44%) 10 3 / 121 (2.48%) 3 6 / 121 (4.96%) 6		

subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Tooth resorption			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 121 (4.13%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Dermatitis contact			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Skin striae			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Joint lock			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	3		
Infections and infestations			

Adenoiditis				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Body tinea				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Bronchitis				
subjects affected / exposed	2 / 121 (1.65%)			
occurrences (all)	3			
COVID-19				
subjects affected / exposed	6 / 121 (4.96%)			
occurrences (all)	6			
Folliculitis				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	4 / 121 (3.31%)			
occurrences (all)	4			
Nasopharyngitis				
subjects affected / exposed	17 / 121 (14.05%)			
occurrences (all)	28			
Otitis media				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Paronychia				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	3 / 121 (2.48%)			
occurrences (all)	4			
Pharyngitis streptococcal				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences (all)	1			

Rhinitis subjects affected / exposed occurrences (all)	4 / 121 (3.31%) 8		
Sinusitis subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2		
Staphylococcal infection subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	7 / 121 (5.79%) 7		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1		
Varicella subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1		
Viral infection subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 121 (4.13%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2019	Amendment 1 •Added monthly visits to assess safety on a more frequent basis (ie, Months 2, 4, 5, 7, 8, 10, and 11). •Added a 30-day safety follow-up phone call to assess AEs occurring during down-titration. •Inclusion criteria for written informed consent were revised to ensure that subjects who reached 18 years of age during the course of the study were appropriately consented. •Clarified exclusion criteria of DSM-5 criteria. •The exclusion criterion of lifetime history was updated to remove the Structured Clinical Interview for DSM-5 Axis-I Disorders, as it was inappropriate for use in the pediatric population. •Added HbA1c laboratory testing for safety purposes. •Visit windows and numbers were added for visit scheduling guidance in the schedule of assessments. A footnote was added to specify that laboratory samples should be obtained while subjects are in a fasting state for best glucose and lipid testing. Another footnote was updated to include height in the vital signs measurements. •The timepoints for laboratory testing and safety assessment were updated to correct the omission of Month 1. •Corrected the name of the investigational product as ecopipam HCl. •Added information regarding the versions of the C&A-GTS-QOL to be used according to the subject's age (6 to 12 years and 13 to 18 years) and clarified that administration of the C&A-GTS-QOL for subjects who turn 13 years of age during the course of the study should continue to be assessed using the version of the scale initially administered. •The definition of AEs was corrected to include subjects from the time of screening. •A correction was made to include reporting of partner pregnancies. •Safety reporting information was corrected and expanded for reference.

14 March 2019	Amendment 2 •Timelines for study period (estimated date of first subject enrolled and last subject completed) were revised to reflect the operational plan. •Language of study objectives was updated for clarity and corrections were made for consistency throughout the protocol and Study design language was updated for clarity. •Added a follow-up visit 14 days after last dose of study medication or early termination to further assess safety parameters. •Additional guidelines were added in inclusion criteria for the timing of rollover from the EBS-101-CL-001 study to ensure proper subject enrollment & all inclusion and exclusion criteria were numbered for easier identification. •Nomenclature for initial visit (Baseline) in study was corrected to check the inclusion and exclusion criteria and use of ecopipam vs ecopipam HCl was clarified throughout the protocol. •Weight bands were corrected & Titration guidelines were specified who changed weight bands to ensure proper transition to new dose. •Updated timepoints for administration of CGI-TS-I. •Correction was made to the number of Phase 1 studies in indications other than TS in Section 5.1.1.4.1 of the protocol. •Clarified that clinical summary included in Section 5.1.1.4.1 of protocol was from Psyadon studies in indications other than TS. •Criteria for study termination were updated to include that all subjects who had a positive response on Question 4 or 5 of the C-SSRS would be discontinued from study without possibility of restarting for safety reasons, and text related to replacement of subjects was removed. •Updated the protocol's schedule of assessments (removed text: "Within 28 days of screening"; Follow-Up visit added 14 days after last dose; note (*) was revised to add guidance for enrollment into study; footnote #1 was updated to include orthostatic heart rate in vital signs; specified fasting state period in footnote# 3). •Subject replacement criteria were removed from subject withdrawal criteria.
13 June 2019	Amendment 3 •The responsible physician was removed because of site communication routed through the Syneos Health Medical Monitor. •Study objectives were revised to include 18 years of age because some subjects may have turned 18 years of age during the EBS-101-CL-001 study and would still be eligible to participate in the EBS-101-OL-001 study. •Text was updated to clarify that follow-up visits would be conducted based on the last dose of study medication and not according to the number of days of participation in the study. •Language was revised to allow for the possibility of IRB/EC differences in requirements for child assent. •Removed exclusion criteria related to attention deficit disorder/ADHD as it is a common co-morbid condition for subjects with TS, to allow a more clinically relevant subject population to be enrolled. •Correction/clarification was made to the exclusion criteria of DSM-5 to reflect the original intention. •The exclusion criteria regarding the review of ECG data at Baseline was updated to highlight the responsibility of the Principal Investigator. •The exclusion criterion regarding "subjects with a first-degree relative with a major depressive episode that resulted in any psychiatric hospitalization or attempted/completed suicide with the exception of a hospitalization for postpartum depression" was removed because subject privacy laws likely preclude collection of this data from subjects not participating in the study. •Additional detail was provided to exclude subjects with febrile seizures. •Exclusion criteria was updated to remove subjects with positive urine drug screen for tetrahydrocannabinol (THC) as feedback from the clinicians indicated that many subjects with TS use medical THC for their condition, and not as a drug of abuse. •Clarified stratification of dosing. •Added text that approval of the medical monitor was required for dosing changes due to a change in a subject's weight band in Section 10.5 of the protocol.

20 November 2019	Amendment 4 •Changed the sponsor signatory. •Clarified background information on TS, ecopipam, and safety in humans. •Added information regarding the risks and benefits of study participation. •Inclusion and exclusion criteria were revised for clarity. •Added new exclusion criteria to exclude subjects with a known hypersensitivity to ecopipam or any of its excipients. •Contraceptive language in the inclusion criteria was revised for consistency with the Clinical Trials Facilitation Group contraception guidelines; the guidelines were added to an appendix. •Provided additional guidance regarding the removal of subjects from the study. •Added new Section 9.3 to the protocol to provide additional information regarding prohibited therapies. •Prohibited medications list was added to the protocol as an appendix
17 April 2020	Amendment 5 •Updated location and telephone information for Emalex Biosciences, Inc. •Inclusion criterion #1 related to major protocol deviations was amended due to the COVID-19 pandemic. Added new exclusion criteria to provide investigators with the ability to ensure that subjects who may not be suitable for the study could be excluded in addition to formalized exclusion criteria. •The language for objectives, study design, and number of subjects was revised accordingly to changes in inclusion and exclusion criteria. •Alternate remote monitoring procedures were implemented for safety purposes in response to the COVID-19 pandemic. •The study timeline was extended due to the COVID-19 pandemic. •Corrected significant typographical error in exclusion criterion #9 (ie, to exclude the subject with history of seizures [excluding febrile seizures that occurred <2 years prior to Screening]). •Exclusion criterion #14 was updated to maintain consistency with the EBS-101-CL-001 study (removed "and/or marijuana"). •Text was added to provide investigators guidance to monitor subjects for signs of abuse, withdrawal, or dependence. •Information updated in Sections 5.2.2.1 and 5.3.1 of the protocol. •Added clarifying language to the criteria for subject discontinuation. •Updated the protocol's schedule of assessments table (added a footnote for alternate remote monitoring procedures for safety purposes in response to the COVID-19 pandemic, removed HbA1c from Month 1, updated footnote #1 to utilize the HbA1c and urine drug screen labs from the previous study included to minimize duplicate testing) •Text was added for study drug accountability as a result of the COVID-19 pandemic. •Additional statistical analyses were included in response to the COVID-19 pandemic (ie, 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).
17 November 2021	Amendment 6 •Added urinalysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported