Clinical trial results:
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

Summary

EudraCT number	2019-000281-37
Trial protocol	DE FR PL
Global end of trial date	23 September 2021

Results information

Result version number	v1 (current)
This version publication date	25 October 2022
First version publication date	25 October 2022

Trial information

Trial identification

Sponsor protocol code	EBS-101-CL-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04007991
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	Clinical contact, Emalex Biosciences Inc., 0 0018477150562, dkim@emalexbiosciences.com
Scientific contact	Clinical contact, Emalex Biosciences Inc., 0 0018477150562, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 2021
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 efficacy of ecopipam tablets in pediatric subjects (aged greater than [>] 6 to less than [<] 18 years) with Tourette's Syndrome (TS).

Protection of trial subjects:

This study was conducted in accordance with the International Council on Harmonisation tripartite guideline on the ethical principles of Good Clinical Practice (ICH E6), and applicable regulatory requirements including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	United States: 117
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	153
EEA total number of subjects	29

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)	53
Adolescents (12-17 years)	100
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 45 sites enrolled subjects in United States, Canada, Germany, France and Poland from 20 July 2019 (first subject first visit) and 23 September 2021 (last subject last visit).

Pre-assignment

Screening details:

A total of 215 subjects were screened, of which 61 subjects were screen failures and 154 subjects were enrolled in the study. Of the 154 enrolled subjects, 153 were randomized in 1:1 ratio to receive ecopipam HCl and placebo.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received matching placebo tablets orally, once, daily over a titration period followed by an 8-week treatment period.

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

Dosage and administration details:

Subjects received matching placebo tablets orally, once daily.

Arm title	Ecopipam

Arm description:

Subjects received a targeted steady-state dose of 2 milligram per kilogram per day (mg/kg/day) of ecopipam HCl tablets orally, once daily based on the body weight over a titration period followed by an 8-week treatment period.

Arm type	Experimental
Investigational medicinal product name	Ecopipam HCl
Investigational medicinal product code	EBS-101
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Ecopipam HCl tablets orally once daily.

Number of subjects in period 1	Placebo	Ecopipam
Started	77	76
Completed	71	66
Not completed	6	10
Consent withdrawn by subject	1	1
Physician decision	1	1
Non-compliance with Study Drug	1	-
Withdrawal by Parent/Caregiver	2	1
Adverse event, non-fatal	-	5
Lost to follow-up	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo tablets orally, once, daily over a titration period followed by an 8-week treatment period.	
Reporting group title	Ecopipam
Reporting group description:	
Subjects received a targeted steady-state dose of 2 milligram per kilogram per day (mg/kg/day) of ecopipam HCl tablets orally, once daily based on the body weight over a titration period followed by an 8-week treatment period.	

Reporting group values	Placebo	Ecopipam	Total
Number of subjects	77	76	153
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	26	27	53
Adolescents (12-17 years)	51	49	100
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	12.6	12.6	
standard deviation	± 2.63	± 2.78	-
Gender categorical			
Units: Subjects			
Female	24	17	41
Male	53	59	112
Race			
Units: Subjects			
White	72	66	138
Black or African American	3	6	9
Asian	2	1	3
American Indian or Alaska Native	0	1	1
Other	0	2	2
Ethnicity			
Units: Subjects			
Hispanic or Latino	11	13	24
Not Hispanic or Latino	66	63	129

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo tablets orally, once, daily over a titration period followed by an 8-week treatment period.	
Reporting group title	Ecopipam
Reporting group description:	
Subjects received a targeted steady-state dose of 2 milligram per kilogram per day (mg/kg/day) of ecopipam HCl tablets orally, once daily based on the body weight over a titration period followed by an 8-week treatment period.	

Primary: Change From Baseline in the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) at Week 12

End point title	Change From Baseline in the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) at Week 12
End point description:	
The YGTSS was a semi-structured clinical interview designed to measure the tic severity. This scale consisted of a tic inventory, with 5 separate rating scales to rate the severity of symptoms, and an impairment ranking. Ratings were made along 5 different dimensions on a scale of 0=none to 5=severe for motor and vocal tics, each including number, frequency, intensity, complexity, and interference. The YGTSS TTS was the summation of the severity scores of motor and vocal tics. The total tic score (TTS) ranged from 0 (none) to 50 (severe) with higher score represent more severe symptoms. A negative change from baseline indicates improvement. The modified intent-to-treat (mITT) set included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline scoring of the YGTSS. Here, "number of subjects analysed" refer to the subjects evaluable for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo	Ecopipam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	74		
Units: Score on a scale				
least squares mean (standard error)	-6.42 (± 1.006)	-9.87 (± 1.062)		

Statistical analyses

Statistical analysis title	Ecopipam vs. Placebo
Statistical analysis description:	
Change from baseline in YGTSS score as a continuous variable was based on mixed model for repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix.	
Comparison groups	Placebo v Ecopipam

Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.011
Method	ANCOVA
Parameter estimate	Difference in Least Square Mean
Point estimate	-3.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.09
upper limit	-0.79
Variability estimate	Standard error of the mean
Dispersion value	1.351

Secondary: Change From Baseline in Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) at Week 12

End point title	Change From Baseline in Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) at Week 12

End point description:

Clinical Global Impression (CGI) scale was used to assess overall severity on a 7-point Likert scale consisted of 2 reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms. The CGI severity scale ranges from 1 = Normal, not at all ill; 2 = Borderline ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill subject. 1 = "normal, not ill at all" to 7 = "extremely ill." A negative change indicates improvement in the condition. The mITT set included all randomised subjects who received at least 1 dose of study drug and had at least 1 post-baseline scoring of the YGTSS. Here, "number of subjects analysed" refer to the subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Ecopipam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	65		
Units: Score on a scale				
least squares mean (standard error)	-0.53 (± 0.130)	-0.91 (± 0.141)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening up to Week 16

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Ecopipam

Reporting group description:

Subjects received a targeted steady-state dose of 2 mg/kg/day of ecopipam HCl tablets orally, once daily based on the body weight over a titration period followed by an 8-week treatment period.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo tablets orally, once, daily over a titration period followed by an 8-week treatment period.

Serious adverse events	Ecopipam	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 76 (2.63%)	1 / 77 (1.30%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Coronavirus infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Ecopipam	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 76 (61.84%)	38 / 77 (49.35%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 76 (0.00%)	3 / 77 (3.90%)	
occurrences (all)	0	3	
Fall			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Muscle strain			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Sunburn			
subjects affected / exposed	2 / 76 (2.63%)	1 / 77 (1.30%)	
occurrences (all)	2	1	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 76 (15.79%)	7 / 77 (9.09%)	
occurrences (all)	16	11	
Somnolence			
subjects affected / exposed	6 / 76 (7.89%)	2 / 77 (2.60%)	
occurrences (all)	6	2	
Dizziness			
subjects affected / exposed	3 / 76 (3.95%)	0 / 77 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 76 (7.89%)	0 / 77 (0.00%)	
occurrences (all)	8	0	
Pyrexia			
subjects affected / exposed	1 / 76 (1.32%)	3 / 77 (3.90%)	
occurrences (all)	1	3	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	4 / 76 (5.26%)	1 / 77 (1.30%)	
occurrences (all)	6	1	
Abdominal pain			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	1 / 76 (1.32%)	2 / 77 (2.60%)	
occurrences (all)	1	2	
Diarrhea			
subjects affected / exposed	1 / 76 (1.32%)	3 / 77 (3.90%)	
occurrences (all)	1	3	
Vomiting			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 76 (5.26%)	0 / 77 (0.00%)	
occurrences (all)	4	0	
Restlessness			
subjects affected / exposed	4 / 76 (5.26%)	0 / 77 (0.00%)	
occurrences (all)	4	0	
Insomnia			
subjects affected / exposed	7 / 76 (9.21%)	1 / 77 (1.30%)	
occurrences (all)	7	1	
Depressed mood			
subjects affected / exposed	3 / 76 (3.95%)	2 / 77 (2.60%)	
occurrences (all)	3	2	
Depression			

subjects affected / exposed	1 / 76 (1.32%)	2 / 77 (2.60%)	
occurrences (all)	1	2	
Irritability			
subjects affected / exposed	3 / 76 (3.95%)	1 / 77 (1.30%)	
occurrences (all)	3	1	
Middle insomnia			
subjects affected / exposed	3 / 76 (3.95%)	1 / 77 (1.30%)	
occurrences (all)	3	1	
Sleep disorder			
subjects affected / exposed	3 / 76 (3.95%)	1 / 77 (1.30%)	
occurrences (all)	3	1	
Tic			
subjects affected / exposed	2 / 76 (2.63%)	2 / 77 (2.60%)	
occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	2 / 76 (2.63%)	1 / 77 (1.30%)	
occurrences (all)	2	1	
Neck pain			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 76 (6.58%)	4 / 77 (5.19%)	
occurrences (all)	5	5	
Coronavirus infection			
subjects affected / exposed	1 / 76 (1.32%)	1 / 77 (1.30%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 76 (2.63%)	4 / 77 (5.19%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2019	Amendment 1: • Two exclusion criteria were clarified to ensure subject eligibility could be determined accurately; • Secondary efficacy endpoints were specified and prioritized; • Clarified when study appointments were to be made and when blood draws should be conducted for pharmacokinetic (PK) evaluations; • Updates to study procedures and schedule of assessments: 30-day Follow-Up call added, Baseline CGI-I and CGI-C deleted as these were not needed, footnotes added to highlight that laboratory samples should be obtained while subjects were in a fasted state and to include height in vital signs; • Statement added to indicate study drug dosing will not change due to changes in weight during the study; • Added HbA1c as a special laboratory parameter; • Correction made to include reporting of partner pregnancies.
28 February 2019	Amendment 2: • Additional assessments added to Week 6 visit to better understand the time course of responses; • Weight bands corrected; • Exclusion on hepatic impairment added to reduce variability in ecopipam exposure • Clarification of pregnancy exclusion criteria; • Clarification of exclusion criteria regarding DSM-5 criteria; • Clarified and specified exclusion criteria regarding the change in YGTSS-TTS score between the Screening and Baseline visits to an absolute percentage change; • Clarified the time period of previous treatments in exclusion criteria; • Added exclusion criteria to exclude subjects who have initiated behavioral therapies; • Added requirement that a subject's Baseline dose will not be adjusted based on subject weight changes; • Reworded key and other secondary efficacy endpoints in order of importance; • Clarified administration of study drug dose during the Week 4 visit; • Corrected clinical summary from Schering-Plough studies and Psyadon studies to be consistent with the Investigator's Brochure; • Added text to stipulate the additional requirement for randomization assignment to be based on weight stratification; • Added clarification for subjects who do not tolerate dose titration and dose instructions; • Clarified when safety assessments will be performed; • Clarified the function and responsibilities of the data safety monitoring board (DSMB) charter, the types of DSMB members for the study, as well as clarified recommendations that the DSMB may make for the study.
28 May 2019	Amendment 3: • Follow-Up visits and Follow-Up contact amended to be based on the last dose of study drug instead of the date of the visit; • Washout period of medications used to treat motor or vocal tics was reduced from 21 days to 14 days to facilitate subject visit scheduling; • Correction/clarification made to the exclusion criteria regarding mood disorders (DSM-5 criteria) to reflect original intention; • Exclusion criteria text on ECG at Screening was updated to reflect the responsibility of the principal investigator in review of ECG data; • Tetrahydrocannabinol was removed from the urine drug screen exclusion criteria; • Exclusion criterion regarding subjects with a first-degree relative with a major depressive episode was deleted; • Exclusionary previous treatments were reworded to match more realistic pediatric TS population treatment scenarios; • Exclusion criterion for subjects who received psychostimulants for the treatment of attention deficit disorder/ attention deficit/hyperactivity disorder (ADHD) was deleted; • Timing of the PK visit after last dose adjusted and text amended for clarity regarding scheduling of PK visits.

25 October 2019	Amendment 4: • Sections 5.2 and 5.3 were created with new subsections for clarity and to provide additional information; • Correction to footnotes in schedule of assessments table; • Inclusion and exclusion criteria were refined for clarity; • Contraception language was revised for consistency with the Clinical Trials Facilitation Group Contraception Guidelines, and the guidelines were added to an appendix; • St. John's Wort was added as an exclusionary medication; • Text on the removal of subjects from the study was revised to provide additional guidance; • Section added to provide additional information regarding prohibited therapies and a; prohibited medications list was added to an appendix; • Text revised to clarify it was the responsibility of the investigator to determine if the blind must be broken for safety reasons.
13 April 2020	Amendment 5: • Alternate remote monitoring procedures were implemented for safety purposes in response to the COVID-19 pandemic; • Inclusion criterion stating the subject has received an adequate trial of nonpharmacological therapy without adequate response was amended to pertain only to subjects enrolled outside of the United States and Canada; • Exclusion criterion regarding subjects who have initiated new behavioral therapies fewer than 10 weeks prior to Baseline was revised to exclude the wording "to treat TS"; • Added an exclusion criterion to provide investigators the ability to ensure that subjects who may not be suitable for the study could be excluded; • Text added to provide investigators guidance to monitor subjects for signs of abuse, and withdrawal or dependence; • Updated information in Sections 5.2 and 5.3; • Updates to schedule of assessments table (urine pregnancy test was added to Day 14 Follow-Up visit and text added to clarify that approval was required for rescreening); • Text added regarding how direct-to-subject shipments of study drug may be necessary as a result of the COVID-19 pandemic; • Efficacy endpoints for change in CGI-TS-I and CaGI-C corrected to begin at Week 4; • Plan for protocol deviations related to the COVID-19 pandemic was specified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported