Clinical trial results:
A double blind, randomized, placebo-controlled, adaptive 14-week Phase IIb trial to evaluate the efficacy and safety of vafidemstat in an adult borderline personality disorder (BPD) population (PORTICO)

Summary

EudraCT number	2020-003469-20
Trial protocol	ES DE BG
Global end of trial date	13 November 2023

Results information

Result version number	v1 (current)
This version publication date	02 January 2025
First version publication date	02 January 2025

Trial information

Trial identification

Sponsor protocol code	CL07-ORY-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04932291
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oryzon Genomics
Sponsor organisation address	Sant Ferrán 74, Cornellà de Llobregat, Spain, 08940
Public contact	Clinical Operations, Oryzon Genomics S.A., 34 93 515 1313, sgutierrez@oryzon.com
Scientific contact	Chief Medical Officer, Oryzon Genomics S.A., 34 93 515 1313, mropacki@oryzon.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	27 June 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 November 2023
Global end of trial reached?	Yes
Global end of trial date	13 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To investigate the efficacy of vafidemstat in the treatment of agitation and aggression in adult BPD patients
- To investigate the efficacy of vafidemstat in the treatment of adult BPD patients

Protection of trial subjects:

No specific protection of trial subjects was put in place

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2021
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	Spain: 17
Country: Number of subjects enrolled	Bulgaria: 28
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	United States: 116
Country: Number of subjects enrolled	Serbia: 13
Worldwide total number of subjects	211
EEA total number of subjects	82

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	211

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Main selection criteria: adult men/ women 18-65 years; DSM-5 diagnostic criteria for BPD met at least 3 months before Screening; AAPI-CR A/A subscale score ≥16 (severity X frequency); sum of A/A subscale severity scores ≥6; mantain pre-screening psychotherapy and permitted concomitant medications, should not initiate them during the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Full analysis set population

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

Dosage and administration details:

During the 12-week, double-blind, randomized, placebo-controlled Treatment period, from Visit 2 to Visit 8, participants were randomized to:
• Vafidemstat: participants received 1 capsule with 1.2 mg/day of vafidemstat from Monday to Friday and 1 capsule of placebo from Saturday to Sunday.
• Placebo: participants received 1 capsule of placebo per day.
During the 2-week, participant-blind, run-out safety follow-up period, from Visit 8 to Visit 9, all participants received 1 capsule of placebo per day.

Arm title	Vafidemstat 1.2 mgr

Arm description:

Full analysis set population

Arm type	Experimental
Investigational medicinal product name	Vafidemstat
Investigational medicinal product code	ORY-2001
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

During the 12-week, double-blind, randomized, placebo-controlled Treatment period, from Visit 2 to Visit 8, participants were randomized to:
• Vafidemstat: participants received 1 capsule with 1.2 mg/day of vafidemstat from Monday to Friday and 1 capsule of placebo from Saturday to Sunday.
• Placebo: participants received 1 capsule of placebo per day.
During the 2-week, participant-blind, run-out safety follow-up period, from Visit 8 to Visit 9, all participants received 1 capsule of placebo per day.

Number of subjects in period 1	Placebo	Vafidemstat 1.2 mgr
Started	105	106
Completed	79	76
Not completed	26	30
Consent withdrawn by subject	8	10
Physician decision	-	3
Adverse event, non-fatal	1	4
Pregnancy	1	-
Subject has Covid-19	-	1
Lost to follow-up	9	9
Lack of efficacy	1	-
Protocol deviation	6	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Full analysis set population	
Reporting group title	Vafidemstat 1.2 mgr
Reporting group description: Full analysis set population	

Reporting group values	Placebo	Vafidemstat 1.2 mgr	Total
Number of subjects	105	106	211
Age categorical			
Full analysis set population			
Units: Subjects			
Adults (18-64 years)	105	106	211
Age continuous			
Full analysis set population			
Units: years			
median	29	31	
inter-quartile range (Q1-Q3)	23 to 37	23 to 40	-
Gender categorical			
Full analysis set population			
Units: Subjects			
Female	80	78	158
Male	25	28	53

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description:	
Full analysis set population	
Reporting group title	Vafidemstat 1.2 mgr
Reporting group description:	
Full analysis set population	

Primary: Difference in the CGI-S A/A from Baseline to average of Weeks 8 to 12	
End point title	Difference in the CGI-S A/A from Baseline to average of Weeks 8 to 12
End point description:	
Change on the Clinical Global Impression-Severity focused on Agitation/Aggression (CGI-S A/A) from Baseline to average of Weeks 8 to 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the placebo arm (full analysis set population)	
End point type	Primary
End point timeframe:	
From Baseline-Week 0 to average of Weeks 8 to 12	

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-1.31 (± 0.111)	-1.47 (± 0.111)		

Statistical analyses

Statistical analysis title	1ary endpoint: CGI-Severity Agitation/Aggression
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2266
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.1

Variability estimate	Standard error of the mean
Dispersion value	0.133

Primary: Difference in the BPDCL-Total Score from Baseline to average of Weeks 8 to 12

End point title	Difference in the BPDCL-Total Score from Baseline to average of Weeks 8 to 12

End point description:

Change on the Borderline Personality Disorder Checklist (BPDL) - Total Score from Baseline to average of Weeks 8 to 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the placebo arm (full analysis set population)

End point type	Primary

End point timeframe:

From Baseline-Week 0 to average of Weeks 8 to 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-30.6 (± 3.449)	-34.0 (± 3.428)		

Statistical analyses

Statistical analysis title	1ary endpoint: BPDCL-Total Score
Comparison groups	Vafidemstat 1.2 mgr v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3839
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	4.34
Variability estimate	Standard error of the mean
Dispersion value	3.941

Secondary: Difference in the BEST-Total Score from Baseline to average of Weeks 8

to 12

End point title	Difference in the BEST-Total Score from Baseline to average of Weeks 8 to 12

End point description:

Change on the Borderline Evaluation of Severity Over Time (BEST) - Total Score from Baseline to average of Weeks 8 to 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

From Baseline-Week 0 to average of Weeks 8 to 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-8.64 (± 1.053)	-11.3 (± 1.047)		

Statistical analyses

Statistical analysis title	2ary endpoint: BEST-Total Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.02
upper limit	-0.32
Variability estimate	Standard error of the mean
Dispersion value	1.189

Secondary: Difference in the BDI-II Total Score from Baseline to average of Weeks 8 to 12

End point title	Difference in the BDI-II Total Score from Baseline to average of Weeks 8 to 12

End point description:

Change on the Beck Depression Inventory – II (BDI-II) - Total Score from Baseline to average of Weeks 8 to 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary
End point timeframe:	
From Baseline-Week 0 to average of Weeks 8 to 12	

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-6.18 (± 1.366)	-8.79 (± 1.354)		

Statistical analyses

Statistical analysis title	2ary endpoint: BDI-II Total Score
Comparison groups	Vafidemstat 1.2 mgr v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0944
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.68
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	1.552

Secondary: Difference in the STAXI-2-Anger Expression Index Raw Score from Baseline to average of Weeks 8 to 12

End point title	Difference in the STAXI-2-Anger Expression Index Raw Score from Baseline to average of Weeks 8 to 12
End point description:	
Change on the State-Trait Anger Expression Inventory 2 (STAXI-2) - Anger Expression Index Raw Score from Baseline to average of Weeks 8 to 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)	
End point type	Secondary
End point timeframe:	
From Baseline-Week 0 to average of Weeks 8 to 12	

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-6.36 (± 1.355)	-8.98 (± 1.345)		

Statistical analyses

Statistical analysis title	2ary endpoint: STAXI-2-Anger Expression Index Raw
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0966
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.72
upper limit	0.48
Variability estimate	Standard error of the mean
Dispersion value	1.569

Secondary: Difference in the STAXI-2-State Anger Scale Raw Score from Baseline to average of Weeks 8 to 12

End point title	Difference in the STAXI-2-State Anger Scale Raw Score from Baseline to average of Weeks 8 to 12

End point description:

Change on the State-Trait Anger Expression Inventory 2 (STAXI-2) - State Anger Scale Raw Score from Baseline to average of Weeks 8 to 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

From Baseline-Week 0 to average of Weeks 8 to 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-4.30 (± 0.882)	-4.87 (± 0.879)		

Statistical analyses

Statistical analysis title	2ary endpoint: STAXI-2-State Anger Scale Raw Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5684
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.53
upper limit	1.39
Variability estimate	Standard error of the mean
Dispersion value	0.991

Secondary: Difference in the STAXI-2-Trait Anger Scale Raw Score from Baseline to average of Weeks 8 to 12

End point title	Difference in the STAXI-2-Trait Anger Scale Raw Score from Baseline to average of Weeks 8 to 12

End point description:

Change on the State-Trait Anger Expression Inventory 2 (STAXI-2) - Trait Anger Scale Raw Score from Baseline to average of Weeks 8 to 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

From Baseline-Week 0 to average of Weeks 8 to 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-3.45 (± 0.643)	-5.47 (± 0.638)		

Statistical analyses

Statistical analysis title	2ary endpoint: STAXI-2-Trait Anger Scale Raw Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0071
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.49
upper limit	-0.56
Variability estimate	Standard error of the mean
Dispersion value	0.742

Secondary: Difference in the STAI-State Anxiety Raw Score from Baseline to average of Weeks 8 to 12

End point title	Difference in the STAI-State Anxiety Raw Score from Baseline to average of Weeks 8 to 12

End point description:

Change on the State-Trait Anxiety Inventory (STAI) - State Anxiety Raw Score from Baseline to average of Weeks 8 to 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

From Baseline-Week 0 to average of Weeks 8 to 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-6.06 (± 1.281)	-7.61 (± 1.281)		

Statistical analyses

Statistical analysis title	2ary endpoint: STAI-State Anxiety Raw Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2901
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.41
upper limit	1.33
Variability estimate	Standard error of the mean
Dispersion value	1.453

Secondary: Difference in the CGI-S A/A over time (from Baseline to Week 12)

End point title	Difference in the CGI-S A/A over time (from Baseline to Week 12)

End point description:

Change over time on the Clinical Global Impression-Severity focused on Agitation/Aggression (CGI-S A/A) , from Baseline to Week 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

Over time: from Baseline-Week 0 to Week 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-1.55 (± 0.138)	-1.76 (± 0.139)		

Statistical analyses

Statistical analysis title	2ary endpoint: CGI-Severity Agitation/Aggression
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2142
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.8
upper limit	4.36
Variability estimate	Standard error of the mean
Dispersion value	4.34

Secondary: Difference in the BPDCL-Total Score over time (from Baseline to Week 12)

End point title	Difference in the BPDCL-Total Score over time (from Baseline to Week 12)

End point description:

Change over time on the Borderline Personality Disorder Checklist (BPDCL), from Baseline to Week 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

Over time: from Baseline-Week 0 to Week 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-31.6 (± 3.724)	-35.8 (± 3.729)		

Statistical analyses

Statistical analysis title	2ary endpoint: BPDCL-Total Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3333
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.8
upper limit	4.36
Variability estimate	Standard error of the mean
Dispersion value	4.34

Secondary: Difference in the BEST-Total Score over time (from Baseline to Week 12)

End point title	Difference in the BEST-Total Score over time (from Baseline to Week 12)

End point description:

Change over time on the Borderline Evaluation of Severity Over Time (BEST)-Total Score, from Baseline to Week 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

Over time: from Baseline-Week 0 to Week 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-9.16 (± 1.128)	-11.9 (± 1.130)		

Statistical analyses

Statistical analysis title	2ary endpoint: BEST-Total Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0384
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.27
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	1.296

Secondary: Difference in the BDI-II Total Score over time (from Baseline to Week 12)

End point title	Difference in the BDI-II Total Score over time (from Baseline to Week 12)

End point description:

Change over time on the Beck Depression Inventory – II (BDI-II) Total Score, from Baseline to Week 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

Over time: from Baseline-Week 0 to Week 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-6.43 (± 1.459)	-8.88 (± 1.456)		

Statistical analyses

Statistical analysis title	2ary endpoint: BDI-II Total Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1473
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.78
upper limit	0.87
Variability estimate	Standard error of the mean
Dispersion value	1.684

Secondary: Difference in the STAXI-2-Anger Expression Index Raw Score over time (from Baseline to Week 12)

End point title	Difference in the STAXI-2-Anger Expression Index Raw Score over time (from Baseline to Week 12)

End point description:

Change over time on the State-Trait Anger Expression Inventory 2 (STAXI-2)-Anger Expression Index Raw Score, from Baseline to Week 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

Over time: from Baseline-Week 0 to Week 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-6.72 (± 1.497)	-9.77 (± 1.491)		

Statistical analyses

Statistical analysis title	2ary endpoint: STAXI-2-Anger Expression Index Raw
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0851
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.53
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	1.761

Secondary: Difference in the STAXI-2-State Anger Scale Raw Score over time (from Baseline to Week 12)

End point title	Difference in the STAXI-2-State Anger Scale Raw Score over time (from Baseline to Week 12)

End point description:

Change over time on the State-Trait Anger Expression Inventory 2 (STAXI-2)-State Anger Scale Raw Score, from Baseline to Week 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

Over time: from Baseline-Week 0 to Week 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-5.41 (± 0.903)	-6.25 (± 0.910)		

Statistical analyses

Statistical analysis title	2ary endpoint: STAXI-2-State Anger Scale Raw Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4157
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.88
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	1.03

Secondary: Difference in the STAXI-2-Trait Anger Scale Raw Score over time (from Baseline to Week 12)

End point title	Difference in the STAXI-2-Trait Anger Scale Raw Score over time (from Baseline to Week 12)

End point description:

Change over time on the State-Trait Anger Expression Inventory 2 (STAXI-2)-Trait Anger Scale Raw Score, from Baseline to Week 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

Over time: from Baseline-Week 0 to Week 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-3.80 (± 0.751)	-5.96 (± 0.750)		

Statistical analyses

Statistical analysis title	2ary endpoint: STAXI-2-Trait Anger Scale Raw Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0158
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.92
upper limit	-0.41
Variability estimate	Standard error of the mean
Dispersion value	0.889

Secondary: Difference in the STAI-State Anxiety Raw Score over time (from Baseline to Week 12)

End point title	Difference in the STAI-State Anxiety Raw Score over time (from Baseline to Week 12)

End point description:

Change over time on the State-Trait Anxiety Inventory (STAI) State Anxiety Raw Score, from Baseline to Week 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

Over time: from Baseline-Week 0 to Week 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-7.21 (± 1.490)	-8.41 (± 1.507)		

Statistical analyses

Statistical analysis title	2ary endpoint: STAI-State Anxiety Raw Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4942
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.64
upper limit	2.25
Variability estimate	Standard error of the mean
Dispersion value	1.745

Secondary: Difference in the STAI-Trait Anxiety Raw Score over time (from Baseline to Week 12)

End point title	Difference in the STAI-Trait Anxiety Raw Score over time (from Baseline to Week 12)

End point description:

Change over time on the State-Trait Anxiety Inventory (STAI) -Trait Anxiety Raw Score from Baseline to Week 12, between the active treatment arm (Vafidemstat 1.2 mgr) and the Placebo arm (full analysis set population)

End point type	Secondary

End point timeframe:

Over time: from Baseline-Week 0 to Week 12

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Arbitary unit				
least squares mean (standard error)	-4.41 (± 1.186)	-5.46 (± 1.142)		

Statistical analyses

Statistical analysis title	2ary endpoint: STAI-Trait Anxiety Raw Score
Comparison groups	Placebo v Vafidemstat 1.2 mgr

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4057
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.54
upper limit	1.44
Variability estimate	Standard error of the mean
Dispersion value	1.262

Secondary: Number of subjects experiencing treatment-emergent adverse events (TEAEs)

End point title	Number of subjects experiencing treatment-emergent adverse events (TEAEs)

End point description:

Number of subjects experiencing treatment-emergent adverse events (TEAEs) in the active treatment arm (Vafidemstat 1.2 mgr) and the placebo arm (safety analysis set population).
Study discontinuation and study drug withdrawal are equivalent: all subjects withdrawn from study drug were discontinued from the study.
AESI: TEAEs of Special Interest.

End point type	Secondary

End point timeframe:

From Baseline-Week 0 to Week 14

End point values	Placebo	Vafidemstat 1.2 mgr		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	106		
Units: Subjects				
Treatment-Emergent SAEs (TESAEs)	0	1		
Treatment-Related TEAEs	33	36		
Treatment-Related TESAEs	0	0		
TEAEs leading to discontinuation/ drug withdrawal	1	5		
TEAEs leading to drug interruption	3	5		
TEAEs by severity	68	61		
Mild	60	51		
Moderate	35	29		
Severe	4	5		
TEAEs by outcome	68	61		
Recovered/ Resolved	66	56		
Not Recovered/ Not Resolved	17	14		
Recovering/ Resolving	9	8		

Recovered/ Resolved with Sequelae	1	0		
Death	0	0		
Unknown	0	0		
Any TEAEs of Special Interest	1	9		
Platelet count decreased	1	8		
Neutrophil count decreased	0	2		
Intentional self-injury	6	1		
COVID-19 TEAEs	6	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment-emergent adverse events reported from Baseline-Week 0 to Week 14	
Adverse event reporting additional description:	
Safety set population	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Safety set population	
Reporting group title	Vafidemstat 1.2 mgr
Reporting group description:	
Safety set population	

Serious adverse events	Placebo	Vafidemstat 1.2 mgr	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 104 (0.00%)	1 / 106 (0.94%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Kidney infection			
subjects affected / exposed	0 / 104 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Vafidemstat 1.2 mgr	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 104 (38.46%)	27 / 106 (25.47%)	
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 104 (16.35%)	13 / 106 (12.26%)	
occurrences (all)	18	16	
Tension headache			

subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 17	5 / 106 (4.72%) 11	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	18 / 104 (17.31%) 22	9 / 106 (8.49%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2021	Modification of study endpoints' evaluation times. Reason: changes on statistical methods. Sample size increased. Reason: changes in study statistical considerations. Amendments to Statistical Methods section. Reason: changes in study statistical considerations. Other minor changes and clarifications in different protocol sections.
12 July 2021	Addition of a paragraph on reproductive and developmental toxicology in Section 1.3. Reason: to provide a more accurate dose justification. Addition of the CSSRS to the list of safety assessments in Section 7.3 (Safety Assessments). Reason: clarification of its safety purpose. Addition of "Overdose should be reported as an adverse event" in Section 8.5. Reason: safety reporting clarification. Amendments to the Statistical Methods section. Reason: to implement a more precise and appropriate statistical methodology. Other minor changes and clarifications added to different protocol sections.
28 September 2021	Update of Concomitant Medication section and addition of new text informing participants of serotoninergic syndrome. Reason: to adhere with regulatory requirements. Update of the Laboratory Safety Assessments section. Reason: to provide clarity on safety requirements. Modification of Statistical Analysis section. Reason: to adhere with regulatory requirements. Update of Study Procedures to include qualitative research data obtention and update of Pharmacokinetic Assessment, only for the US sites. Reason: to adhere with regulatory requirements.
08 August 2022	Changes on several includion and exclusion criteria. Reason: flexibilization of the conditions for participant inclusion. Update of Concomitant Medication section. Reason: to account for the potential addiction to benzodiazepines. Update of Statistical Methods and Study Design sections to further detail the Interim analysis strategy. Reason: to implement regulatory suggestions.
24 May 2023	Update of Statistical Analysis & Determination of Sample Size sections regarding effect size and sample size: increase of sample size. Reason: to implement regulatory suggestions. Modifications in the Concomitant Medication and Follow-up of Participants after AEs sections. Reason: to provide clarity on participants safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported