Clinical trial results:
An unicenter, open-label, 1-arm, 8-week study to evaluate the efficacy, safety and tolerability of ORY-2001 in aggression in adult population with Adult Attention Deficit Hyperactivity Disorder (ADHD), Borderline Personality Disorder (BPD), Autism Spectrum Disorder (ASD).

Summary

EudraCT number	2018-002140-88
Trial protocol	ES
Global end of trial date	22 October 2019

Results information

Result version number	v1 (current)
This version publication date	08 August 2021
First version publication date	08 August 2021

Trial information

Trial identification

Sponsor protocol code	CL04-ORY-2001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Oryzon Genomics S.A.
Sponsor organisation address	Carrer de Sant Ferran, 74, Oryzon, CORNELLA DE LLOBREGAT, Spain, 08940
Public contact	Michael Ropacki, Chief Medical Officer, CNS Clinical & Product Development, Oryzon Genomics S.A., +34 93 515 1313, mropacki@oryzon.com
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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	22 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability and efficacy of vafidemstat in adult population with Adult attention deficit hyperactivity disorder (ADHD), Borderline Personality Disorder (BPD) or Autism Spectrum Disorder (ASD)

Protection of trial subjects:

In accordance with European Union RGPD 2016/679 of 27 April, 2016 the data were processed in accordance with the specifications outlined by the local law to ensure that requirements regarding personal data protection are met. If an external organization processed data on behalf of Oryzon, a contractual procedure was signed between Oryzon and the external organization to ensure compliance with the above-mentioned legislation. If applicable, the participation of patients in this study was reported to the appropriate local data protection agencies, in accordance with European Union RGPD 2016/679 of 27 April 2016 and Country-specific guidelines and laws (Spanish Organic Law 3/2018 of 5 December).

Background therapy:

Patients entered the study under their usual ADHD, BPD or ASD treatment, on a stable dose, for at least 4-months prior to the Screening Visit (until approval of protocol amendment on 19/03/2019) and for at least 1-month prior to the Screening, thereafter. In addition, patients had to remain on this stable treatment dose for their condition (i.e. the patient’s individual maintenance dose for ADHD, BPD or ASD) during the Screening Period and throughout the study.

Evidence for comparator:

N/A

Actual start date of recruitment	08 October 2018
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	Spain: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	32
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 35 subjects were screened to obtain a total of 32 enrolled patients. Recruitment was planned to be equally stratified by disease cohorts. The first 18 patients continued to be distributed as planned and the distribution of the remaining patients was flexible between the three cohorts.

Pre-assignment

Screening details:

A total of 35 patients were screened at Vall d'Hebron Universitari Hospital. Of those, 3 patients were considered screen failures and therefore discarded. A total of 32 patients were included in the study based on having received at least one dose of the IMP and completed, at least, one study visit.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Adult Attention Deficit Hyperactivity Disorder (ADHD)

Arm description:

Adult Attention Deficit Hyperactivity Disorder (ADHD)

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

Dosage and administration details:

Vafidemstat was administered orally, 1.2 mg/day, as a single capsule, fiw, in a 5 days on / 2 days off schedule.

Arm title	Borderline Personality Disorder (BPD)

Arm description:

Borderline Personality Disorder (BPD)

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

Dosage and administration details:

Vafidemstat was administered orally, 1.2 mg/day, as a single capsule, fiw, in a 5 days on / 2 days off schedule.

Arm title	Autism Spectrum Disorder (ASD)

Arm description:

Autism Spectrum Disorder (ASD)

Arm type	Experimental

Investigational medicinal product name	Vafidemstat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Vafidemstat was administered orally, 1.2 mg/day, as a single capsule, fiw, in a 5 days on / 2 days off schedule.

Number of subjects in period 1	Adult Attention Deficit Hyperactivity Disorder (ADHD)	Borderline Personality Disorder (BPD)	Autism Spectrum Disorder (ASD)
Started	12	13	7
Completed	8	9	6
Not completed	4	4	1
other reasons	2	3	1
Lost to follow-up	2	1	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	32	32	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 33.12 ± 12.17	 -	
Gender categorical Units: Subjects			
Female	18	18	
Male	14	14	
Education Units: Subjects			
Some school	6	6	
School graduate	17	17	
College graduate	8	8	
University degree	1	1	
Race Units: Subjects			
Caucasian	27	27	
Black	0	0	
Asian	0	0	
Latin	5	5	
Height Units: meter arithmetic mean standard deviation	 1.7 ± 0.1	 -	
Weight Units: kilogram(s) arithmetic mean standard deviation	 75.32 ± 23.14	 -	
BMI Units: kilogram(s)/square meter arithmetic mean standard deviation	 25.86 ± 6.77	 -	

Subject analysis sets

Subject analysis set title	All groups
Subject analysis set type	Full analysis

Subject analysis set description:
ADHD, BPD, ASD

Reporting group values	All groups		
Number of subjects	32		
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	33.12		
standard deviation	± 12.17		
Gender categorical Units: Subjects			
Female	18		
Male	14		
Education Units: Subjects			
Some school	6		
School graduate	17		
College graduate	8		
University degree	1		
Race Units: Subjects			
Caucasian	27		
Black	0		
Asian	0		
Latin	5		
Height Units: meter			
arithmetic mean	1.7		
standard deviation	± 0.1		
Weight Units: kilogram(s)			
arithmetic mean	75.32		
standard deviation	± 23.14		
BMI Units: kilogram(s)/square meter			
arithmetic mean	25.86		
standard deviation	± 6.77		

End points

End points reporting groups

Reporting group title	Adult Attention Deficit Hyperactivity Disorder (ADHD)
Reporting group description: Adult Attention Deficit Hyperactivity Disorder (ADHD)	
Reporting group title	Borderline Personality Disorder (BPD)
Reporting group description: Borderline Personality Disorder (BPD)	
Reporting group title	Autism Spectrum Disorder (ASD)
Reporting group description: Autism Spectrum Disorder (ASD)	

Subject analysis set title	All groups
Subject analysis set type	Full analysis
Subject analysis set description: ADHD, BPD, ASD	

Primary: Number and severity of Treatment Emergent Adverse Events (TEAEs) up to Week 8

End point title	Number and severity of Treatment Emergent Adverse Events (TEAEs) up to Week 8[1]
End point description: In the study, all Adverse Events (AEs) were Treatment Emergent Adverse Events (TEAEs) and all the Adverse Reactions (ARs) were Treatment Emergent Adverse Reactions (TEARs).	
End point type	Primary
End point timeframe: From baseline and during the 8-week Treatment Period followed by a 4-week Safety Follow-up Period after the last dose intake of the study drug.	

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: Number of cases, events and percentage of adverse events (AEs), adverse reactions (ARs) and serious ARs were calculated for the entire duration of the study (up to end of follow-up) as aggregated numbers.

End point values	All groups			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: number				
Severity - MILD	96			
Severity - MODERATE	0			
Severity - SEVERE	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number, frequency and severity of Serious TEAEs up to Week 8

End point title	Number, frequency and severity of Serious TEAEs up to Week 8

	[2]

End point description:

End point type	Primary

End point timeframe:

From baseline and during the 8-week Treatment Period followed by a 4-week Safety Follow-up Period after the last dose intake of the study drug.

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: There were no Serious Adverse Events (SAEs) during the study, up to Visit 7 (Week 8) or the follow-up period

End point values	All groups			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: number	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of withdrawn patients due to TEAEs up to Week 8

End point title	Number of withdrawn patients due to TEAEs up to Week 8[3]

End point description:

End point type	Primary

End point timeframe:

From Baseline and throughout the 8-week Treatment Period.

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: None of the patients withdrew due to safety related events.

End point values	All groups			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: number	0			

Statistical analyses

No statistical analyses for this end point

Primary: Physical examination, vital signs and ECG parameters - Change from baseline to Week 8

End point title	Physical examination, vital signs and ECG parameters - Change from baseline to Week 8[4]

End point description:

End point type	Primary

End point timeframe:

Vital signs were measured as part of the physical examination conducted at the Baseline Visit as well as part of the Safety Assessments at each study visit.

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 comparison between groups was performed for this endpoint. The difference between Visit 7(Week 8)/EoS and Visit 1 (Baseline) data was summarized using means, medians, minimum, maximum, standard deviations (SD) and inter-quartile-range. The variations observed were evaluated in terms of "clinically relevant changes".

End point values	Adult Attention Deficit Hyperactivity Disorder (ADHD)	Borderline Personality Disorder (BPD)	Autism Spectrum Disorder (ASD)	All groups
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12	13	7	32
Units: unit(s)				
arithmetic mean (standard deviation)				
SBP (mm Hg)	3.25 (± 11.16)	-6.78 (± 9.15)	-3 (± 10.86)	-2.3 (± 10.79)
DBP (mm Hg)	6.62 (± 12.94)	-3.89 (± 5.4)	-4.5 (± 8.64)	-0.39 (± 10.41)
Supine SBP (mm Hg)	3.25 (± 11.16)	-6.78 (± 9.15)	-3 (± 10.86)	-2.3 (± 10.79)
Supine DBP (mm Hg)	6.62 (± 12.94)	-3.89 (± 5.4)	-4.5 (± 8.64)	-0.39 (± 10.41)
HR (bpm)	2.38 (± 12.25)	-1 (± 15.11)	1.83 (± 6.91)	0.91 (± 12)
Body temperature (°C)	-0.09 (± 0.22)	-0.06 (± 0.16)	0.02 (± 0.24)	-0.05 (± 0.2)
RR (bpm)	0.38 (± 1.41)	0.33 (± 2)	0.17 (± 1.17)	0.3 (± 1.55)
Resting RR (bpm)	0.38 (± 1.41)	0.33 (± 2)	-0.5 (± 1.05)	0.13 (± 1.58)
ECG - HR (bpm)	2.5 (± 10.62)	-0.33 (± 12.44)	-0.33 (± 4.13)	0.65 (± 9.9)
ECG - PR (ms)	-4.75 (± 19.09)	-3.33 (± 9.22)	-1.67 (± 6.86)	-3.39 (± 12.61)
ECG - QRS (ms)	-2.5 (± 7.84)	-1.33 (± 3)	-1.67 (± 3.44)	-1.83 (± 5.08)
ECG - QT (ms)	-9.5 (± 22.92)	-1.56 (± 26.62)	10 (± 6.07)	-1.3 (± 22.19)
ECG - QTc (ms)	-0.75 (± 16.53)	-2.33 (± 14.47)	10 (± 17.5)	1.43 (± 16.14)

Statistical analyses

No statistical analyses for this end point

Primary: Clinical laboratory parameters - Haematology - Change from baseline to Week 8

End point title	Clinical laboratory parameters - Haematology - Change from baseline to Week 8[5]

End point description:

End point type	Primary

End point timeframe:

At the Baseline Visit as well as part of the Safety Assessments at each study visit.

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 comparison between groups has been performed for this endpoint. The difference between Visit 7(Week 8)/EoS and Visit 1 (Baseline) data was summarized using means, medians, minimum, maximum, standard deviations (SD) and inter-quartile-range. The variations observed were evaluated in terms of "clinically relevant changes".

End point values	Adult Attention Deficit Hyperactivity Disorder (ADHD)	Borderline Personality Disorder (BPD)	Autism Spectrum Disorder (ASD)	All groups
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12	13	7	32
Units: unit(s)				
arithmetic mean (standard deviation)				
RBC (10e12/L)	0.07 (± 0.11)	-0.1 (± 0.16)	-0.1 (± 0.24)	-0.04 (± 0.18)
Hb (g/dL)	-0.01 (± 0.56)	-0.37 (± 0.66)	-0.13 (± 0.48)	-0.18 (± 0.58)
Haematocrit (%)	0.86 (± 1.21)	-0.38 (± 1.37)	-1.17 (± 2.21)	-0.15 (± 1.71)
MCV (fL)	0.27 (± 2.26)	1.21 (± 3.13)	-0.68 (± 1.88)	0.39 (± 2.57)
MCH (pg)	-0.54 (± 0.86)	-0.1 (± 0.96)	0.35 (± 1.01)	-0.13 (± 0.96)
MCHC (g/dL)	-0.71 (± 0.84)	-0.6 (± 1.81)	0.63 (± 1.17)	-0.32 (± 1.44)
WBC (10e9/L)	0.42 (± 1.14)	-0.55 (± 1.34)	-1.03 (± 0.69)	-0.33 (± 1.24)
Neutrophils (%)	-3.44 (± 8.28)	-8.74 (± 12.81)	-7.7 (± 3.91)	-6.63 (± 9.53)
Lymphocytes (%)	0.74 (± 8.28)	5.24 (± 10.25)	3.35 (± 3.04)	3.18 (± 8.12)
Monocytes (%)	2.21 (± 1.96)	1.18 (± 1.73)	3.08 (± 3.81)	2.03 (± 2.5)
Eosinophyls (%)	0.52 (± 2.31)	2.13 (± 2.98)	1.05 (± 0.68)	1.29 (± 2.36)
Basophils (%)	-0.04 (± 0.15)	0.19 (± 0.21)	0.22 (± 0.2)	0.12 (± 0.22)
Neutrophils (10e9/L)	-0.12 (± 0.81)	-1.01 (± 1.71)	-1.08 (± 0.5)	0.72 (± 1.24)
Lymphocytes (absolute) (10e9/L)	0.25 (± 0.75)	0.28 (± 0.55)	-0.07 (± 0.39)	0.18 (± 0.59)
Monocytes (absolute) (10e9/L)	0.19 (± 0.19)	0.07 (± 0.14)	0.07 (± 0.14)	0.11 (± 0.16)
Eosinophils (absolute) (10e9/L)	0.09 (± 0.18)	0.16 (± 0.21)	0.07 (± 0.05)	0.11 (± 0.17)
Basophils (absolute) (10e9/L)	0 (± 0.08)	0.04 (± 0.07)	0.03 (± 0.05)	0.03 (± 0.07)
Platelets (10e9/L)	-37.5 (± 37.36)	-29.56 (± 49.16)	-29.67 (± 96)	-32.35 (± 58.58)

Statistical analyses

No statistical analyses for this end point

Primary: Clinical laboratory parameters - Biochemistry - Change from baseline to Week 8

End point title	Clinical laboratory parameters - Biochemistry - Change from baseline to Week 8[6]

End point description:

End point type	Primary

End point timeframe:

At the Baseline Visit as well as part of the Safety Assessments at each study visit.

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 comparison between groups has been performed for this endpoint. The difference between Visit 7(Week 8)/EoS and Visit 1 (Baseline) data was summarized using means, medians, minimum, maximum, standard deviations (SD) and inter-quartile-range. The variations observed were evaluated in terms of "clinically relevant changes".

End point values	Adult Attention Deficit Hyperactivity Disorder (ADHD)	Borderline Personality Disorder (BPD)	Autism Spectrum Disorder (ASD)	All groups
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12	13	7	32
Units: unit(s)				
arithmetic mean (standard deviation)				
Glucose (mg/dL)	-5.12 (± 9.78)	-7.44 (± 13.3)	8 (± 21.23)	-2.61 (± 15.49)
HbA1c (%)	0 (± 0)	0 (± 0)	-0.2 (± 0)	-0.2 (± 0)
Urea (mg/dL)	-1 (± 5.26)	-0.11 (± 6.53)	-3.33 (± 4.68)	-1.26 (± 5.57)
Creatinine (mg/dL)	0.01 (± 0.12)	-0.03 (± 0.09)	0.04 (± 0.07)	0 (± 0.1)
Total bilirubin (mg/dL)	-0.1 (± 0.21)	0.12 (± 0.31)	-0.01 (± 0.12)	0.01 (± 0.25)
Conjugated bilirubin (mg/dL)	-0.01 (± 0.04)	0.02 (± 0.06)	0 (± 0.04)	0 (± 0.05)
Sodium (mmol/L)	-0.69 (± 2.34)	-0.6 (± 3.08)	-0.32 (± 1.18)	-0.56 (± 2.35)
Potassium (mmol/L)	-0.02 (± 0.21)	0.15 (± 0.39)	0.14 (± 0.1)	0.09 (± 0.28)
Phosphate (mg/dL)	-0.21 (± 0.7)	-0.33 (± 0.58)	0.05 (± 0.31)	-0.19 (± 0.57)
Calcium (mg/dL)	-0.23 (± 0.39)	-0.23 (± 0.31)	-0.12 (± 0.23)	-0.2 (± 0.31)
AST (U/L)	0.88 (± 4.42)	2.89 (± 7.85)	-12 (± 19.6)	-1.7 (± 12.48)
ALT (U/L)	-3.12 (± 9.08)	1.89 (± 8.24)	-28.5 (± 42.81)	-7.78 (± 25.11)
Alkaline phosphatase (U/L)	-3.62 (± 6)	4 (± 13.62)	-4.17 (± 5.12)	-0.78 (± 10.01)
GGT (U/L)	1.62 (± 5.13)	4.56 (± 8.44)	-1.5 (± 6.35)	1.96 (± 7.04)
Creatinine kinase (U/L)	-31 (± 96.19)	-60.57 (± 164.24)	-26.75 (± 38.45)	-42.88 (± 117.54)
LDH (U/L)	90 (± 103.41)	30.86 (± 90.02)	3.75 (± 144.35)	35.79 (± 105.84)
Amylase (U/L)	1.6 (± 10.55)	-0.29 (± 9.32)	-10.75 (± 6.24)	-2.31 (± 9.91)
Cholesterol (mg/dL)	-12.5 (± 37.06)	-8 (± 28.4)	-21.83 (± 8.3)	-13.17 (± 27.89)
Triglycerides (mg/dL)	-23.25 (± 28.28)	1.56 (± 9.74)	-33.83 (± 89.76)	-16.3 (± 48.5)
Total protein (g/dL)	-0.01 (± 0.35)	-0.1 (± 0.4)	-0.2 (± 0.24)	-0.1 (± 0.34)
Albumin (g/dL)	0.03 (± 0.18)	-0.09 (± 0.26)	-0.03 (± 0.14)	-0.05 (± 0.2)
CRP (mg/dL)	0.31 (± 0.47)	0.02 (± 0.39)	-0.04 (± 0.11)	0.1 (± 0.38)

Statistical analyses

No statistical analyses for this end point

Primary: Use of concomitant medication throughout the study period

End point title	Use of concomitant medication throughout the study period[7]

End point description:

End point type	Primary

End point timeframe:

Since Screening Period for up to 1 week and an 8-week Treatment Period followed by a 4-week Safety Follow-up Period after the last dose intake of the study drug.

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 has been applied to this endpoint

End point values	All groups			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: number				
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	1			
ANALGESICS	15			
ANTIBACTERIALS FOR SYSTEMIC USE	2			
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGIC	1			
ANTIEPILEPTICS	11			
ANTIHISTAMINES FOR SYSTEMIC USE	3			
ANTIHYPERTENSIVES	1			
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	11			
COUGH AND COLD PREPARATIONS	1			
DRUGS USED IN DIABETES	1			
LIPID MODIFYING AGENTS	1			
MINERAL SUPPLEMENTS	1			
MUSCLE RELAXANTS	1			
PSYCHOANALEPTICS	16			
PSYCHOLEPTICS	15			
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	1			
TONICS	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Neuropsychiatric Inventory Questionnaire - Agitation/Aggression (NPI-A/A) - Change from Baseline to Week 8

End point title	Neuropsychiatric Inventory Questionnaire - Agitation/Aggression (NPI-A/A) - Change from Baseline to Week 8

End point description:

Change from Visit 1 (Baseline) to Visit 7/EoS (Week 8) was calculated, for each patient, for all groups (aggregated data) and the different groups (cohorts), as the difference between Visit 7 (Week 8)/EoS and Visit 1 (Baseline) in the PPS population. Results were presented as score’s mean values and standard deviation (SD) wit p-values calculated as Wilcoxon Sign-rank Test. After 8 weeks of treatment the difference between Visit 7/EoS and Visit 1 (Baseline) for the NPI-A/A for all groups (aggregated

data), was statistically significant (p<0.0001). There was also a statistically significant difference in NPI-A/A score after 8 weeks of treatment with vafidemstat for each of the different cohorts (ADHD, BPD and ADS), with p-values being p=0.007, p=0.0068 and p=0.0175, respectively.

End point type	Secondary

End point timeframe:

From Visit 1 (Baseline) to Visit 7(Week 8)/EoS

End point values	Adult Attention Deficit Hyperactivity Disorder (ADHD)	Borderline Personality Disorder (BPD)	Autism Spectrum Disorder (ASD)	All groups
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	9	6	23
Units: unit(s)				
arithmetic mean (standard deviation)	-3.88 (± 1.55)	-2.78 (± 1.64)	-2.67 (± 1.21)	-3.13 (± 1.55)

Statistical analyses

No statistical analyses for this end point

Secondary: Neuropsychiatric Inventory Questionnaire (NPI) - Total NPI - Change from Baseline to Week 8

End point title	Neuropsychiatric Inventory Questionnaire (NPI) - Total NPI - Change from Baseline to Week 8

End point description:

Change from Visit 1 (Baseline) to Visit 7/EoS (Week 8) was calculated, for each patient, for all groups (aggregated data) and the different groups (cohorts), as the difference between Visit 7 (Week 8)/EoS and Visit 1 (Baseline) in the PPS population. Results were presented as score's mean values, standard deviation (SD) and p-values calculated as Wilcoxon Sign-rank Test. After 8 weeks of treatment, the difference between Visit 7/EoS and Visit 1 (Baseline) for the Total NPI score for all groups (aggregated data), was statistically significant (p<0.0001). After 8 weeks of treatment, there was a statistically significant difference in the Total NPI for each of the cohorts: p=0.0065 for ADHD; p=0.0124 for BPD; and p=0.0178 for ASD.

End point type	Secondary

End point timeframe:

From Visit 1 (Baseline) to Visit 7(Week 8)/EoS

End point values	Adult Attention Deficit Hyperactivity Disorder (ADHD)	Borderline Personality Disorder (BPD)	Autism Spectrum Disorder (ASD)	All groups
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	9	6	23
Units: unit(s)				
arithmetic mean (standard deviation)	-4.88 (± 1.89)	-5.56 (± 5.13)	-6 (± 2.53)	-5.43 (± 3.51)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression of Severity (CGI-S) aggression scale - Change from Baseline to Week 8

End point title	Clinical Global Impression of Severity (CGI-S) aggression scale - Change from Baseline to Week 8

End point description:

Change from Visit 1 (Baseline) to Visit 7/EoS (Week 8) was calculated, for each patient, for all groups (aggregated data) and the different groups (cohorts), as the difference between Visit 7 (Week 8)/EoS and Visit 1 (Baseline) in the PPS population. Results were presented as score's mean values and standard deviation (SD) wit p-values calculated as Wilcoxon Sign-rank Test. After 8 weeks of treatment the difference between Visit 7/EoS and Visit 1 (Baseline) in the CGI-S score for all groups (aggregated data) was statistically significant ($p<0.0001$). There was also a statistically significant difference after 8 weeks of treatment with vafidemstat for each of the different cohorts (ADHD, BPD and ADS); p-values: $p=0.0066$, $p=0.0064$ and $p=0.016$, respectively.

End point type	Secondary

End point timeframe:

From Visit 1 (Baseline) to Visit 7(Week 8)/EoS

End point values	Adult Attention Deficit Hyperactivity Disorder (ADHD)	Borderline Personality Disorder (BPD)	Autism Spectrum Disorder (ASD)	All groups
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	9	6	23
Units: unit(s)				
arithmetic mean (standard deviation)	-1.88 (± 0.83)	-1.78 (± 0.97)	-1.5 (± 0.55)	-1.74 (± 0.81)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression of Improvements (CGI-I) aggression scale - Change from Baseline to Week 8

End point title	Clinical Global Impression of Improvements (CGI-I) aggression scale - Change from Baseline to Week 8

End point description:

Change from Visit 1 (Baseline) to Visit 7/EoS (Week 8) was calculated, for each patient, for all groups (aggregated data) and the different groups (cohorts), as the difference between Visit 7 (Week 8)/EoS and Visit 1 (Baseline) in the PPS population. Results were presented as score's mean values and

standard deviation (SD) wit p-values calculated as Wilcoxon Sign-rank Test. After 8 weeks of treatment the difference between Visit 7/EoS and Visit 1 (Baseline) in the CGI-I score for all groups (aggregated data) was statistically significant (p<0.0001). There was also a statistically significant difference after 8 weeks of treatment with vafidemstat for each of the different cohorts (ADHD, BPD and ADS); p-values: p=0.0066, p=0.0155 and p=0.016, respectively.

End point type	Secondary

End point timeframe:

From Visit 1 (Baseline) to Visit 7(Week 8)/EoS

End point values	Adult Attention Deficit Hyperactivity Disorder (ADHD)	Borderline Personality Disorder (BPD)	Autism Spectrum Disorder (ASD)	All groups
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	8	6	22
Units: unit(s)				
arithmetic mean (standard deviation)	-2.12 (± 0.83)	-1.5 (± 1.07)	-2.5 (± 0.55)	-2 (± 0.93)

Statistical analyses

No statistical analyses for this end point

Secondary: Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) - Changes from baseline to Week 8

End point title	Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) - Changes from baseline to Week 8[8]

End point description:

Change from Visit 1 (Baseline) to Visit 7/EoS (Week 8) was calculated, for each patient, in the ADHD group (cohort), as the difference between Visit 7 (Week 8)/EoS and Visit 1 (Baseline) in the PPS population. Results were presented as score's mean values and standard deviation (SD) wit p-values calculated as Wilcoxon Sign-rank Test. The difference between Visit 7/EoS and Visit 1 (Baseline) in the ADHD-RS score, after 8 weeks of treatment with vafidemstat, was statistically significant (p=0.0496).

End point type	Secondary

End point timeframe:

From Visit 1 (Baseline) to Visit 7 (Week 8)/EoS

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: ADHD patients only

End point values	Adult Attention Deficit Hyperactivity Disorder (ADHD)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: unit(s)				
arithmetic mean (standard deviation)	-5 (± 7.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Borderline Personality Disease Checklist (BPDCL) - Change from Baseline to Week 8

End point title	Borderline Personality Disease Checklist (BPDCL) - Change from Baseline to Week 8[9]

End point description:

Change from Visit 1 (Baseline) to Visit 7/EoS (Week 8) was calculated, for each patient, in the BPD group (cohort), as the difference between Visit 7 (Week 8)/EoS and Visit 1 (Baseline) in the PPS population. Results were presented as score's mean values and standard deviation (SD) wit p-values calculated as Wilcoxon Sign-rank Test. The difference between Visit 7/EoS and Visit 1 (Baseline) in the BPDCL Total score, after 8 weeks of treatment with vafidemstat, was statistically significant (p=0.0022).

End point type	Secondary

End point timeframe:

From Visit 1 (Baseline) to Visit 7 (Week 8)/EoS

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: BPD patients only

End point values	Borderline Personality Disorder (BPD)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: unit(s)				
arithmetic mean (standard deviation)	-38.56 (± 29.5)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetics: trough vafidemstat plasma levels (Ctrough) on Days 1, 5, and 26 (Visit 1, 2 and 5)

End point title	Pharmacokinetics: trough vafidemstat plasma levels (Ctrough) on Days 1, 5, and 26 (Visit 1, 2 and 5)

End point description:

Descriptive summary statistics of the Ctrough values observed in all groups (aggregated data) and the different cohorts was conducted (shown below). There were no statistically significant differences among the Ctrough values observed for each of the different cohorts (ADHD, BPD and ADS) during the course of the study, nor there were on day 5 and 26 (Wilcoxon Sign-rank Test), suggesting that steady state concentrations were reached within the first week of treatment in all cases.

End point type	Other pre-specified

End point timeframe:

Days 1, 5, and 26 (Visit 1, Visit 2, and Visit 5)

End point values	Adult Attention Deficit Hyperactivity Disorder (ADHD)	Borderline Personality Disorder (BPD)	Autism Spectrum Disorder (ASD)	All groups
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	11	12	7	30
Units: unit(s)				
arithmetic mean (standard deviation)				
Day 1	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)
Day 5	4127.13 (± 2102.36)	5279.92 (± 3681.31)	7321.89 (± 7699.89)	5378.70 (± 4819.95)
Day 26	4566.84 (± 3386.00)	3767.58 (± 2363.21)	7121.25 (± 8838.12)	4892.17 (± 5199.39)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacodynamics: Change over time in LSD1 target engagement (TE) in PBMCs on Days 1, 5, and 26 (Visit 1, 2 and 5)

End point title	Pharmacodynamics: Change over time in LSD1 target engagement (TE) in PBMCs on Days 1, 5, and 26 (Visit 1, 2 and 5)

End point description:

A descriptive summary of the LSD1-TE values observed in all groups and the different cohorts is shown below. There were no statistically significant differences among the LSD1-TE values observed for each of the different cohorts (ADHD, BPD and ADS) during the course of the study, nor there were on day 5 and 26 (Wilcoxon Sign-rank Test), suggesting that the maximum effect was reached within the first week of treatment in all patients.

End point type	Other pre-specified

End point timeframe:

Days 1, 5, and 26 (Visit 1, Visit 2, and Visit 5)

End point values	Adult Attention Deficit Hyperactivity Disorder (ADHD)	Borderline Personality Disorder (BPD)	Autism Spectrum Disorder (ASD)	All groups
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	11	7	28
Units: unit(s)				
arithmetic mean (standard deviation)				
Day 1	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)
Day 5	75.01 (± 9.46)	76.65 (± 4.63)	68.13 (± 16.52)	73.67 (± 11.35)

Day 26	71.92 (± 12.60)	61.96 (± 26.69)	75.60 (± 10.98)	68.98 (± 19.98)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Throughout the study period	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	All groups
Reporting group description: ADHD, BPD, ASD	

Serious adverse events	All groups		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All groups		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 32 (75.00%)		
Investigations			
Blood creatine phosphokinase abnormal			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Platelet count decreased			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Electrocardiogram QT interval abnormal			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Amylase abnormal			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Blood lactate dehydrogenase abnormal			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	6		
Poisoning			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Toxicity to various agents			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Surgical and medical procedures			
Female sterilisation			
subjects affected / exposed[1]	1 / 18 (5.56%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 32 (31.25%)		
occurrences (all)	26		
Sensory disturbance			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Somnolence			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Presyncope			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		

General disorders and administration site conditions			
Discomfort			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 7		
Insomnia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 4		
Abnormal behaviour subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 2		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Muscle contracture subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Myalgia subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Pain in extremity subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Infections and infestations			
Influenza subjects affected / exposed occurrences (all)	8 / 32 (25.00%) 9		
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 4		
Oral herpes subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Herpes virus infection subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Bronchitis			

subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The study included 18 female subjects

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2019	The study was designed to study the effect of vafidemstat on aggression across 5 different CNS conditions (ADHD, BPD, ASD, AD and DLB). After the protocol amendment approval, the AD and DLB cohorts were dropped for lack of recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported