Clinical trial results:
A multicentre, multinational, randomised, double-blind, placebo-controlled, 3-arm, 24-week parallel-group study to evaluate the safety, tolerability and preliminary efficacy of ORY-2001 in patients with mild-moderate Alzheimer's Disease. ETHERAL Study

Summary

EudraCT number	2017-004893-32
Trial protocol	ES FR GB
Global end of trial date	28 August 2020

Results information

Result version number	v1 (current)
This version publication date	19 March 2022
First version publication date	19 March 2022

Trial information

Trial identification

Sponsor protocol code	CL03-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	C/Sant Ferran 74, Cornellà de Llobregat, Spain, 08940
Public contact	Clinical Operations, Oryzon Genomics S.A., 34 935151313, sgutierrez@oryzon.com
Scientific contact	Clinical Operations, Oryzon Genomics S.A., 34 935151313, sgutierrez@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	21 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 August 2020
Global end of trial reached?	Yes
Global end of trial date	28 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of two doses of vafidemstat (ORY-2001) in subjects with mild-moderate Alzheimer's Disease

Protection of trial subjects:

Subjects were free to discontinue their participation in the study at any time. An independent Data Monitoring Committee (DMC) reviewed unblinded safety data throughout the study. All subjects, except for those who withdraw consent, completed a Safety Follow-up Visit 30 days after last dose of vafidemstat. For subjects who withdrew their consent, a safety assessment conducted by a physician outside the scope of this study was also recommended 4 weeks after treatment discontinuation.

Background therapy:

AChEI (donepezil, rivastigmine, or galantamine)

Evidence for comparator:

Placebo was the comparator in the Treatment period. No comparator was used during the Extension period.

Actual start date of recruitment	02 April 2018
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: 52
Country: Number of subjects enrolled	United Kingdom: 55
Country: Number of subjects enrolled	France: 10
Worldwide total number of subjects	117
EEA total number of subjects	62

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)	18
From 65 to 84 years	92
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

A total of 17 centers in France (n=3), Spain (n=6) and The United Kingdom (n=8) recruited subjects in this study, whereas 16 centers enrolled subjects.

Pre-assignment

Screening details:

A Screening Period for up to 4 weeks before the Treatment Period was allowed. Randomization was stratified by cognitive impairment severity at the Screening Visit (MMSE score: 16-19 vs. 20-26). A total of 218 subjects were screened and 117 subjects were randomized and treated.

Period 1

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

Blinding implementation details:

Initially, all patients were randomised in a 2:2:1 ratio. After Amendment No. 3, patients were randomised in a 1:1:2 ratio from the 41st patient onwards (i.e. 85 patients). Blinding was only to be broken for serious, unexpected, and related AEs that required immediate medical treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Vafidemstat 0.6 mg

Arm description: -

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:

Swedish orange coloured size 3 capsules (hydroxypropyl methylcellulose shells) loaded directly with 0.6 mg ORY-2001 drug substance without addition of excipients, and by means of Xcelodose® filling technology. The subjects were instructed to take orally one capsule of IMP fiw, e.g. once-a-day from Monday to Friday (in the morning)

Arm title	Vafidemstat 1.2 mg

Arm description: -

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:

Swedish orange coloured size 3 capsules (hydroxypropyl methylcellulose shells) loaded directly with 1.2 mg ORY-2001 drug substance without addition of excipients, and by means of Xcelodose® filling technology. The subjects were instructed to take orally one capsule of IMP fiw, e.g. once-a-day from Monday to Friday (in the morning)

Arm title	Placebo

Arm description: -	
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:

Swedish orange coloured size 3 capsules (hydroxypropyl methylcellulose shells) loaded directly with cellulose microcristalline by means of Xcelodose® filling technology. The subjects were instructed to take orally one capsule of IMP fiw, e.g. once-a-day from Monday to Friday (in the morning)

Number of subjects in period 1	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo
Started	38	34	45
Completed	31	28	38
Not completed	7	6	7
Consent withdrawn by subject	2	2	2
Physician decision	-	1	1
Adverse event, non-fatal	2	2	3
Other	1	1	-
Protocol deviation	2	-	1

Period 2

Period 2 title	Extension Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

During the Extension Period, subjects in the placebo arm during the Treatment Period were re-allocated in one of the two different dose levels of vafidemstat in a 1:1 ratio.
This Extension Period was considered open as all subjects were under active treatment and the results were unblinded after the last subject last visit in the Treatment Period. However, IMP labelling remained blinded during the Extension Period.

Arms

Are arms mutually exclusive?	Yes
Arm title	Early Start 0.6 mg

Arm description:

Treatment with vafidemstat 0.6 mg during Treatment Period and Extension Period

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:

Swedish orange coloured size 3 capsules (hydroxypropyl methylcellulose shells) loaded directly with 0.6 mg ORY-2001 drug substance without addition of excipients, and by means of Xcelodose® filling technology. The subjects were instructed to take orally one capsule of IMP fiw, e.g. once-a-day from Monday to Friday (in the morning)

Arm title	Early Start 1.2 mg

Arm description:

Treatment with vafidemstat 1.2 mg during Treatment Period and Extension Period

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:

Swedish orange coloured size 3 capsules (hydroxypropyl methylcellulose shells) loaded directly with 1.2 mg ORY-2001 drug substance without addition of excipients, and by means of Xcelodose® filling technology. The subjects were instructed to take orally one capsule of IMP fiw, e.g. once-a-day from Monday to Friday (in the morning)

Arm title	Delayed Start 0.6 mg

Arm description:

Treated with Placebo during Treatment Period, and treated with vafidemstat 0.6 mg during Extension Period

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:

Swedish orange coloured size 3 capsules (hydroxypropyl methylcellulose shells) loaded directly with 0.6 mg ORY-2001 drug substance without addition of excipients, and by means of Xcelodose® filling technology. The subjects were instructed to take orally one capsule of IMP fiw, e.g. once-a-day from Monday to Friday (in the morning)

Arm title	Delayed Start 1.2 mg

Arm description:

Treated with Placebo during Treatment Period, and treated with vafidemstat 1.2 mg during Extension Period

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:

Swedish orange coloured size 3 capsules (hydroxypropyl methylcellulose shells) loaded directly with 1.2 mg ORY-2001 drug substance without addition of excipients, and by means of Xcelodose® filling

technology. The subjects were instructed to take orally one capsule of IMP fiw, e.g. once-a-day from Monday to Friday (in the morning)

Number of subjects in period 2[1]	Early Start 0.6 mg	Early Start 1.2 mg	Delayed Start 0.6 mg
Started	29	27	18
Completed	25	23	17
Not completed	4	4	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	3	4	1

Number of subjects in period 2[1]	Delayed Start 1.2 mg
Started	19
Completed	16
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 97 subjects completed the Treatment Period and 93 subjects constituted the Extension Period SAF2 population. Out of the 4 subjects completing the Treatment Period but not continuing in the Extension Period, 3 discontinued the study due to and AE (1 subject of each the ES 0.6 mg, ES 1.2 mg and DS 0.6 mg groups), and 1 discontinued due to withdrawal by subject (ES 0.6 mg group).

Baseline characteristics

Reporting groups	
Reporting group title	Vafidemstat 0.6 mg
Reporting group description: -	
Reporting group title	Vafidemstat 1.2 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo
Number of subjects	38	34	45
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Only the FAS population results are available			
Units: years			
arithmetic mean	72.5	71.9	73.5
standard deviation	± 8.0	± 8.0	± 6.1
Gender categorical			
Units: Subjects			
Female	25	18	24
Male	13	16	21

Reporting group values	Total		
Number of subjects	117		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		

Age continuous			
Only the FAS population results are available			
Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	67		
Male	50		

Subject analysis sets

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population includes all subjects who received at least one dose of the study IMP. Safety summaries were performed on the safety set

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

This analysis set includes all randomized subjects who received at least one dose of the IMP and completed at least one test assessing the clinical domains of AD (CMAI, AES-C, ADAS-Cog14, CSDD, Cogstate, MMSE or CDR) with an available score, for at least one visit after baseline

Subject analysis set title	PPS1
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized subjects of the FAS who completed at least one test assessing the clinical domains of AD (CMAI, AES-C, ADAS-Cog14, CSDD, Cogstate, MMSE or CDR) with available scores at Week 24, and who were deemed to have no major protocol violations until Week 24 that could interfere with the objectives of this study

Subject analysis set title	SAF2
Subject analysis set type	Safety analysis

Subject analysis set description:

This safety population includes all subjects who received at least one dose of the study IMP from visit 10 until visit 17 or EoS (after visit 10). Safety summaries for Extension period were performed based on the safety set 2

Subject analysis set title	PPS2
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized subjects of the FAS who completed at least one test assessing the clinical domains of AD (CMAI, AES-C, ADAS-Cog14, CSDD, Cogstate, MMSE or CDR) with available scores at Week 48, and who were deemed to have no major protocol violations until Week 48 that could interfere with the objectives of this study

Reporting group values	SAF	FAS	PPS1
Number of subjects	117	115	96
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years)			

Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Only the FAS population results are available			
Units: years arithmetic mean standard deviation	±	72.7 ± 7.3	±
Gender categorical Units: Subjects			
Female	67	65	
Male	50	50	

Reporting group values	SAF2	PPS2	
Number of subjects	93	66	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Only the FAS population results are available			
Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Vafidemstat 0.6 mg
Reporting group description: -	
Reporting group title	Vafidemstat 1.2 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Early Start 0.6 mg
Reporting group description: Treatment with vafidemstat 0.6 mg during Treatment Period and Extension Period	
Reporting group title	Early Start 1.2 mg
Reporting group description: Treatment with vafidemstat 1.2 mg during Treatment Period and Extension Period	
Reporting group title	Delayed Start 0.6 mg
Reporting group description: Treated with Placebo during Treatment Period, and treated with vafidemstat 0.6 mg during Extension Period	
Reporting group title	Delayed Start 1.2 mg
Reporting group description: Treated with Placebo during Treatment Period, and treated with vafidemstat 1.2 mg during Extension Period	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population includes all subjects who received at least one dose of the study IMP. Safety summaries were performed on the safety set	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: This analysis set includes all randomized subjects who received at least one dose of the IMP and completed at least one test assessing the clinical domains of AD (CMAI, AES-C, ADAS-Cog14, CSDD, Cogstate, MMSE or CDR) with an available score, for at least one visit after baseline	
Subject analysis set title	PPS1
Subject analysis set type	Per protocol
Subject analysis set description: All randomized subjects of the FAS who completed at least one test assessing the clinical domains of AD (CMAI, AES-C, ADAS-Cog14, CSDD, Cogstate, MMSE or CDR) with available scores at Week 24, and who were deemed to have no major protocol violations until Week 24 that could interfere with the objectives of this study	
Subject analysis set title	SAF2
Subject analysis set type	Safety analysis
Subject analysis set description: This safety population includes all subjects who received at least one dose of the study IMP from visit 10 until visit 17 or EoS (after visit 10). Safety summaries for Extension period were performed based on the safety set 2	
Subject analysis set title	PPS2
Subject analysis set type	Per protocol
Subject analysis set description: All randomized subjects of the FAS who completed at least one test assessing the clinical domains of AD (CMAI, AES-C, ADAS-Cog14, CSDD, Cogstate, MMSE or CDR) with available scores at Week 48, and who were deemed to have no major protocol violations until Week 48 that could interfere with the objectives of this study	

Primary: Number of TEAEs

End point title	Number of TEAEs[1]

End point description:

Overall number of TEAEs.
TEAEs reported during the Treatment Period are summarized here for the 3 applicable groups in the SAF population.
TEAEs reported during the Extension Period are summarized here for the 4 applicable groups in the SAF2 population.

End point type	Primary

End point timeframe:

Up to Week 24 (Treatment Period) and from Week 24 to Week 48 (Extension Period)

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: N/A

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: TEAEs	139	156	131	63

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	SAF
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	117
Units: TEAEs	65	18	58	426

End point values	SAF2			
Subject group type	Subject analysis set			
Number of subjects analysed	93			
Units: TEAEs	204			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Severe TEAEs

End point title	Number of Severe TEAEs[2]

End point description:

Severe TEAEs reported during the Treatment Period are summarized here for the 3 applicable groups in the SAF population.
Severe TEAEs reported during the Extension Period are summarized here for the 4 applicable groups in the SAF2 population.

End point type	Primary

End point timeframe:

Up to Week 24 (Treatment Period) and from Week 24 to Week 48 (Extension Period)

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: N/A

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Severe TEAEs	2	3	5	5

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	SAF
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	117
Units: Severe TEAEs	1	2	3	10

End point values	SAF2			
Subject group type	Subject analysis set			
Number of subjects analysed	93			
Units: Severe TEAEs	11			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of TEAEs

End point title	Incidence of TEAEs[3]

End point description:

TEAEs reported during the Treatment Period are summarized here for the 3 applicable groups in the SAF population.
TEAEs reported during the Extension Period are summarized here for the 4 applicable groups in the SAF2 population.

End point type	Primary

End point timeframe:

Up to Week 24 (Treatment Period) and from Week 24 to Week 48 (Extension 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: N/A

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: TEAEs per subject-years of follow-up				
arithmetic mean (standard deviation)	9.23 (± 8.04)	11.99 (± 12.26)	7.51 (± 8.30)	5.27 (± 4.34)

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	SAF
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	117
Units: TEAEs per subject-years of follow-up				
arithmetic mean (standard deviation)	8.20 (± 11.79)	3.56 (± 7.13)	7.00 (± 5.00)	9.37 (± 9.64)

End point values	SAF2			
Subject group type	Subject analysis set			
Number of subjects analysed	93			
Units: TEAEs per subject-years of follow-up				
arithmetic mean (standard deviation)	6.14 (± 7.89)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in vital signs

End point title	Change in vital signs[4]

End point description:

The analysis of vital signs did not reveal any relevant clinically significant trend.

End point type	Primary

End point timeframe:

Change from baseline to Week 24 (Treatment Period) and Week 48 (Extension Period)

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: N/A

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	SAF
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	117
Units: Subjects	27	18	19	117

End point values	SAF2			
Subject group type	Subject analysis set			
Number of subjects analysed	93			
Units: Subjects	93			

Statistical analyses

No statistical analyses for this end point

Primary: Change in ECG parameters

End point title	Change in ECG parameters[5]

End point description:

The analysis of ECG did not reveal any relevant clinically significant trend.

End point type	Primary

End point timeframe:

Change from baseline to Week 24 (Treatment Period) and Week 48 (Extension Period)

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: N/A

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	SAF
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	117

Units: Subjects	27	18	19	117

End point values	SAF2			
Subject group type	Subject analysis set			
Number of subjects analysed	93			
Units: Subjects	93			

Statistical analyses

No statistical analyses for this end point

Primary: Change in clinical laboratory parameters

End point title	Change in clinical laboratory parameters[6]

End point description:

The analysis of laboratory parameters for hematology and biochemistry did not reveal any relevant clinically significant trend.

End point type	Primary

End point timeframe:

Change from baseline to Week 24 (Treatment Period) and Week 48 (Extension Period)

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: N/A

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	SAF
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	117
Units: Subjects	27	18	19	117

End point values	SAF2			
Subject group type	Subject analysis set			
Number of subjects analysed	93			
Units: Subjects	93			

Statistical analyses

No statistical analyses for this end point

Primary: Concomitant medications

End point title	Concomitant medications[7]

End point description:

End point type	Primary

End point timeframe:

Up to Week 24 (Treatment Period) and from Baseline to Week 48 (Extension Period)

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: N/A

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	SAF
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	117
Units: Subjects	27	18	19	117

End point values	SAF2			
Subject group type	Subject analysis set			
Number of subjects analysed	93			
Units: Subjects	93			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohen-Mansfield Agitation Inventory (CMAI) score

End point title	Cohen-Mansfield Agitation Inventory (CMAI) score

End point description:

Over the 24-week Treatment Period, no improvements across secondary endpoints were observed in the vafidemstat treatment groups compared to placebo. Consistent results were observed during the overall trial (48-weeks).

End point type	Secondary

End point timeframe:

Change from baseline to Week 24 (Treatment Period) and Week 48 (Extension Period)
Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115
Units: subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Secondary: Apathy Evaluation Scale - Clinician (AES-C) score

End point title	Apathy Evaluation Scale - Clinician (AES-C) score

End point description:

Over the 24-week Treatment Period, no improvements across secondary endpoints were observed in the vafidemstat treatment groups compared to placebo. Consistent results were observed during the overall trial (48-weeks).

End point type	Secondary

End point timeframe:

Change from baseline to Week 24 (Treatment Period) and Week 48 (Extension Period)
Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115
Units: Subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Secondary: Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score

End point title	Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score

End point description:

Over the 24-week Treatment Period, no improvements across secondary endpoints were observed in the vafidemstat treatment groups compared to placebo. Consistent results were observed during the overall trial (48-weeks).

End point type	Secondary

End point timeframe:

Change from baseline to Week 12, Week 24 (Treatment Period) and Week 48 (Extension Period)
Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115
Units: Subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Secondary: Computerised Cognitive Test battery (Cogstate) score

End point title	Computerised Cognitive Test battery (Cogstate) score

End point description:

Over the 24-week Treatment Period, no improvements across secondary endpoints were observed in the vafidemstat treatment groups compared to placebo. Consistent results were observed during the overall trial (48-weeks).

End point type	Secondary

End point timeframe:

Change from baseline to Week 12, Week 24 (Treatment Period) and Week 48 (Extension Period)
Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115
Units: Subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Secondary: Mini-Mental State Examination (MMSE) score

End point title	Mini-Mental State Examination (MMSE) score

End point description:

Over the 24-week Treatment Period, no improvements across secondary endpoints were observed in the vafidemstat treatment groups compared to placebo. Consistent results were observed during the overall trial (48-weeks).

End point type	Secondary

End point timeframe:

Change from baseline to Week 24 (Treatment Period) and Week 48 (Extension Period)
Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115
Units: Subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Dementia Rating Scale (CDR) scores

End point title	Clinical Dementia Rating Scale (CDR) scores

End point description:

Over the 24-week Treatment Period, no improvements across secondary endpoints were observed in the vafidemstat treatment groups compared to placebo. Consistent results were observed during the overall trial (48-weeks).

End point type	Secondary

End point timeframe:

Change from baseline to Week 24 (Treatment Period) and Week 48 (Extension Period)
Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115

Units: Subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Secondary: Cornell Scale for Depression in Dementia (CSDD) score

End point title	Cornell Scale for Depression in Dementia (CSDD) score

End point description:

Over the 24-week Treatment Period, no improvements across secondary endpoints were observed in the vafidemstat treatment groups compared to placebo. Consistent results were observed during the overall trial (48-weeks).

End point type	Secondary

End point timeframe:

Change from baseline to Week 24 (Treatment Period) and Week 48 (Extension Period)
Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115
Units: Subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cerebrospinal Fluid Biomarkers (PD)

End point title	Cerebrospinal Fluid Biomarkers (PD)

End point description:

The analysis of CSF biomarkers showed no treatment differences in any CSF parameters over the Treatment Period, except for YKL-40, which results in a statistical difference between study arms (p=0.0104). ANCOVA-Least square Means shows that placebo treatment leads to an increase of the CSF levels of YKL-40 at Week 24 compared to baseline (p=0.0006) due to inflammatory progression, while

vafidemstat treatment impedes this increase and no differences from baseline were observed at both treatment arms.
No differences between study arms were observed in YKL-40 biomarker during the Extension Period once all groups were assigned to vafidemstat treatment although the YKL-40 levels were reduced in all arms to similar levels observed in the vafidemstat-treated subjects during the Treatment Period.

End point type	Other pre-specified

End point timeframe:

Change from screening to Week 24 (Treatment Period) and Week 48 (Extension Period)
Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115
Units: Subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Magnetic Resonance Imaging (MRI) parameters

End point title	Magnetic Resonance Imaging (MRI) parameters

End point description:

The MRI parameters showed similar trends across the 3 studied groups over the Treatment Period, only observing a statistically significant effect of the treatment in the superior lateral ventricle LH and RH volumes % of intracranial volume (icv), and the superior lateral ventricles normative percentile. The MRI values showed similar trends across the 4 studied groups over the full study period, only observing a statistically significant effect of the treatment in the superior lateral ventricle LH volume % of icv and the cerebellum RH volume % of icv.

End point type	Other pre-specified

End point timeframe:

Change from baseline to Week 24 (Treatment Period) and Week 48 (Extension Period)
Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115
Units: Subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Dependence Scale score

End point title	Dependence Scale score

End point description:

Over the 24-week Treatment Period, no improvements in the Dependence Scale score were observed in the vafidemstat treatment groups compared to placebo. Consistent results were observed during the overall trial (48-weeks).

End point type	Other pre-specified

End point timeframe:

Change from baseline to Week 24 (Treatment Period) and Week 48 (Extension Period)
Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115
Units: Subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Other pre-specified: EuroQOL five dimensions questionnaire (EQ-5D-5L) score

End point title	EuroQOL five dimensions questionnaire (EQ-5D-5L) score

End point description:

Over the 24-week Treatment Period, no improvements in the EQ-5D-5L score were observed in the vafidemstat treatment groups compared to placebo. Consistent results were observed during the overall trial (48-weeks).

End point type	Other pre-specified

End point timeframe:

Change from baseline to Week 12, Week 24 (Treatment Period) and Week 48 (Extension Period) Change over time

End point values	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo	Early Start 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	34	45	29
Units: Subjects	38	34	45	29

End point values	Early Start 1.2 mg	Delayed Start 0.6 mg	Delayed Start 1.2 mg	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	18	19	115
Units: Subjects	27	18	19	115

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 24 (Treatment Period) and from Week 24 to Week 48 (Extension Period)

Adverse event reporting additional description:

The described 'Non-serious adverse events' results comprise all the TEAEs (serious+non-serious).
TEAEs reported during the Treatment Period are summarized here for the 3 applicable groups in the SAF population.
TEAEs reported during the Extension Period are summarized here for the 4 applicable groups in the SAF2 population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Vafidemstat 0.6 mg
Reporting group description:	
Only TEAEs reported during Treatment Period (up to Week 24)	
Reporting group title	Vafidemstat 1.2 mg
Reporting group description:	
Only TEAEs reported during Treatment Period (up to Week 24)	
Reporting group title	Placebo
Reporting group description:	
Only TEAEs reported during Treatment Period (up to Week 24)	
Reporting group title	Early Start 0.6 mg
Reporting group description:	
Only TEAEs reported during Extension Period (Week 24 to Week 48)	
Reporting group title	Early Start 1.2 mg
Reporting group description:	
Only TEAEs reported during Extension Period (Week 24 to Week 48)	
Reporting group title	Delayed Start 0.6 mg
Reporting group description:	
Only TEAEs reported during Extension Period (Week 24 to Week 48)	
Reporting group title	Delayed Start 1.2 mg
Reporting group description:	
Only TEAEs reported during Extension Period (Week 24 to Week 48)	

Serious adverse events	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 38 (7.89%)	4 / 34 (11.76%)	4 / 45 (8.89%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			

subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Penile squamous cell carcinoma			
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Coronary Artery Stenosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant hypertension			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrial fibrillation			
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia with Lewy bodies			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Upper Gastrointestinal Hemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Early Start 0.6 mg	Early Start 1.2 mg	Delayed Start 0.6 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 29 (10.34%)	1 / 27 (3.70%)	1 / 18 (5.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			

subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Penile squamous cell carcinoma			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Coronary Artery Stenosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant hypertension			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrial fibrillation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 29 (0.00%)	1 / 27 (3.70%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia with Lewy bodies			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Upper Gastrointestinal Hemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Delayed Start 1.2 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			

subjects affected / exposed	0 / 19 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Penile squamous cell carcinoma				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Glioma				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Foot fracture				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Coronary Artery Stenosis				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant hypertension				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Atrial fibrillation			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dementia with Lewy bodies			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Upper Gastrointestinal Hemorrhage			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Vafidemstat 0.6 mg	Vafidemstat 1.2 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 38 (97.37%)	32 / 34 (94.12%)	37 / 45 (82.22%)
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	4 / 38 (10.53%)	2 / 34 (5.88%)	2 / 45 (4.44%)
occurrences (all)	4	2	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	5 / 45 (11.11%)
occurrences (all)	1	1	5
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	1 / 45 (2.22%)
occurrences (all)	2	2	1
Delusion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	0 / 45 (0.00%)
occurrences (all)	2	2	0
Disorientation			
subjects affected / exposed	3 / 38 (7.89%)	1 / 34 (2.94%)	0 / 45 (0.00%)
occurrences (all)	3	1	0
Depression			
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	1 / 45 (2.22%)
occurrences (all)	0	2	1
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 38 (5.26%)	4 / 34 (11.76%)	1 / 45 (2.22%)
occurrences (all)	2	8	1
Neutrophil count decreased			
subjects affected / exposed	1 / 38 (2.63%)	5 / 34 (14.71%)	0 / 45 (0.00%)
occurrences (all)	1	5	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	2 / 45 (4.44%)
occurrences (all)	1	2	2
Blood pressure increased			
subjects affected / exposed	3 / 38 (7.89%)	1 / 34 (2.94%)	1 / 45 (2.22%)
occurrences (all)	3	1	1

Upper respiratory tract infection			
subjects affected / exposed	3 / 38 (7.89%)	0 / 34 (0.00%)	2 / 45 (4.44%)
occurrences (all)	3	0	2
C-reactive protein increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	2 / 45 (4.44%)
occurrences (all)	1	1	2
Haemoglobin decreased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	6 / 38 (15.79%)	2 / 34 (5.88%)	5 / 45 (11.11%)
occurrences (all)	7	3	5
Fall			
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	4 / 45 (8.89%)
occurrences (all)	0	3	6
Contusion			
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	3 / 45 (6.67%)
occurrences (all)	1	0	4
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	1 / 45 (2.22%)
occurrences (all)	0	4	2
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	1 / 45 (2.22%)
occurrences (all)	2	6	1
Dizziness			
subjects affected / exposed	2 / 38 (5.26%)	0 / 34 (0.00%)	2 / 45 (4.44%)
occurrences (all)	2	0	2
Somnolence			
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	2 / 45 (4.44%)
occurrences (all)	1	1	2
Blood and lymphatic system disorders			
Hypertension			

subjects affected / exposed	2 / 38 (5.26%)	1 / 34 (2.94%)	2 / 45 (4.44%)
occurrences (all)	3	1	2
Lymphopenia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	1 / 45 (2.22%)
occurrences (all)	2	1	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	3 / 45 (6.67%)
occurrences (all)	2	2	5
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	2 / 45 (4.44%)
occurrences (all)	1	1	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 38 (7.89%)	1 / 34 (2.94%)	3 / 45 (6.67%)
occurrences (all)	3	1	3
Musculoskeletal pain			
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	0 / 45 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 38 (13.16%)	4 / 34 (11.76%)	1 / 45 (2.22%)
occurrences (all)	5	4	1
Urinary tract infection			
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	2 / 45 (4.44%)
occurrences (all)	1	2	2
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)	4 / 34 (11.76%)	1 / 45 (2.22%)
occurrences (all)	0	5	1
Cellulitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 34 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	2 / 38 (5.26%)	3 / 34 (8.82%)	0 / 45 (0.00%)
occurrences (all)	2	3	0

Non-serious adverse events	Early Start 0.6 mg	Early Start 1.2 mg	Delayed Start 0.6 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 29 (79.31%)	24 / 27 (88.89%)	10 / 18 (55.56%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 29 (3.45%)	1 / 27 (3.70%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Delusion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 27 (3.70%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Confusional state			
subjects affected / exposed	0 / 29 (0.00%)	1 / 27 (3.70%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Disorientation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	1 / 29 (3.45%)	1 / 27 (3.70%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 29 (6.90%)	2 / 27 (7.41%)	0 / 18 (0.00%)
occurrences (all)	3	2	0
Neutrophil count decreased			

subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 27 (3.70%)	1 / 18 (5.56%)
occurrences (all)	0	1	2
Blood pressure increased			
subjects affected / exposed	1 / 29 (3.45%)	2 / 27 (7.41%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 27 (3.70%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	0 / 29 (0.00%)	2 / 27 (7.41%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Haemoglobin decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	2 / 29 (6.90%)	1 / 27 (3.70%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Contusion			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	0 / 29 (0.00%)	1 / 27 (3.70%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dizziness			

subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Hypertension			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 27 (3.70%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 29 (3.45%)	2 / 27 (7.41%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 29 (10.34%)	1 / 27 (3.70%)	1 / 18 (5.56%)
occurrences (all)	3	1	1
Urinary tract infection			
subjects affected / exposed	2 / 29 (6.90%)	4 / 27 (14.81%)	1 / 18 (5.56%)
occurrences (all)	2	4	1
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 29 (0.00%)	0 / 27 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 27 (3.70%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 29 (0.00%)	2 / 27 (7.41%)	0 / 18 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Delayed Start 1.2 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 19 (84.21%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Delusion			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Confusional state			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Disorientation			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Depression			

subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Investigations Platelet count decreased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) Blood pressure increased subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) C-reactive protein increased subjects affected / exposed occurrences (all) Haemoglobin decreased subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0 1 / 19 (5.26%) 1 0 / 19 (0.00%) 0		
Injury, poisoning and procedural complications Overdose subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Cardiac disorders			

Supraventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0 1 / 19 (5.26%) 1 0 / 19 (0.00%) 0		
Blood and lymphatic system disorders Hypertension subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0 1 / 19 (5.26%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	 2 / 19 (10.53%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all) Cellulitis subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 4 4 / 19 (21.05%) 5 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2018	The main protocol modifications emerged after thorough review of the statistical considerations in order not to underestimate the true treatment effect in comparison to the placebo. These considerations included an increase of the sample size from 90 randomized subjects to 125 randomized subjects, and a switch in the randomization scheme from a 2:2:1 (vafidemstat 0.6 mg/day: vafidemstat 1.2 mg/day:placebo) to a 1:1:2 scheme. Specifically, the ETHERAL trial started with a randomization scheme of 2:2:1 between two doses of vafidemstat (0.6 and 1.2 mg) and placebo during the first 6 months treatment period. However, for the following reasons a randomization ratio of 1:1:2 led to a more informative study: 1. Preclinical studies suggested that both doses should have similar therapeutic effect. If the safety and efficacy profiles of the two vafidemstat arms were similar, then a comparison of the pooled vafidemstat arms vs. the placebo group could be more powerful with a 1:1:2 allocation ratio. This combined comparison analysis was finally not performed 2. The placebo group subjects were actually under the standard of care and were expected to have an improvement. A larger proportion of subjects assigned to the placebo group and with re-allocation in the extension period allowed a more efficient within subject comparison within the placebo 3. In case future investigations with vafidemstat were carried out with a Bayesian design, with room to borrow information from previous studies, having a more balanced vafidemstat to placebo assignment in the current study may be more efficient Other changes made to the protocol were: • Planned dates of the last subject first visit (from 3Q 2018 to 1Q 2019) and the last subject last visit (from 3Q 2019 to 1Q 2020) • Accountability of the AChEI (concomitant chronic medication used by all the subjects), from being tracked in the same way of the Investigational Medical Product to being tracked as the other concomitant medications
07 January 2019	Protocol modifications have emerged from a thorough review, where the introduction of some modifications was implemented in order to clarify items that were not previously explained with sufficient detail. The following modifications were performed: • Clarification in definition of fertile female for the inclusion criterion number 12 • Clarification of exclusion criteria number 7 and 8 • Amendment of exclusion criterion number 11 to facilitate recruitment by accommodating the wash-out period to the common criteria in clinical trials • Clarification of window period between visits • Clarification of the blood extractions to be taken during the study • Addition of two Cogstate practice assessments before baseline • Clarification of the subjects re-screened • Clarification of two criteria for removing subjects from therapy or assessment • Clarification of information given to the subject about the storage and handling of Investigational Medicinal Product • Clarification of the treatment compliance • Clarification of the order of the efficacy assessments and the administration of the Investigational Medicinal Product • Clarification of when a clinical laboratory abnormality should be documented as an adverse event

29 April 2019	The following modifications were performed: • Inclusion of an exploratory objective, and the corresponding endpoints, to document APOE genotype in the study's participants as well as examine any associated treatment differences. Finally, none of the planned APOE genotype relationship analyses were performed • Clarification of the Extension Period as an open period because all subjects will be on active treatment and results will be unblinded after the last subject last visit in the 24 week double blind placebo-controlled Treatment Period • Inclusion of an optional blood sample test at any point throughout the study, although baseline collection is recommended, for APOE genotyping • Amendment of inclusion criterion number 10: AD treatment-naïve subjects as eligible participants in the study (only in centers located in France and UK) • Clarification of AChEI compliance assessment as only would apply to subjects with AChEI at the Screening Visit • Amendment of withdrawal criterion about changes in the concomitant medication to make it apply to both AD treatment-naïve subjects and subjects with AChEI at the Screening Visit • Amendment of the statistical issues due to the inclusion of the APOE genotyping, and AD treatment-naïve subjects as eligible participants This protocol amendment also included changes in the study administrative structure

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported