Clinical trial results:
A single-center, open-label, single-arm, 13-week study to evaluate the efficacy, safety and tolerability of ORY-2001 in aggression in Alzheimer's Disease (AD) – REIMAGINE-AD

Summary

EudraCT number	2019-001436-54
Trial protocol	ES
Global end of trial date	17 August 2020

Results information

Result version number	v1 (current)
This version publication date	23 September 2023
First version publication date	23 September 2023

Trial information

Trial identification

Sponsor protocol code	CL06-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, CORNELLA DE LLOBREGAT, Spain, 08940
Public contact	Michael Ropacki, Chief Medical Officer CNS, Oryzon Genomics S.A., Oryzon Genomics S. A., 34 93 515 13 13, mropacki@oryzon.com
Scientific contact	Michael Ropacki, Chief Medical Officer CNS, Oryzon Genomics S.A., Oryzon Genomics S. A., 34 93 515 13 13, mropacki@oryzon.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of ORY-2001 in aggression in an AD population

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: -

Evidence for comparator: -

Actual start date of recruitment	17 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	1
From 65 to 84 years	12

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

It was planned that approximately 15 patients were screened in one single center to obtain a total of 8-12 subjects. A total of 13 patients were screened and 12 subjects were included in the study.

Pre-assignment

Screening details:

This Phase IIa study was a single center, open-label, single arm study with a 1-week Screening Period and no study related procedures, including any screening procedures, were performed before the PI had obtained written informed consent from the patient and/or his/her legal representative and the close relative/caregiver.

Period 1

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

Arms

Arm title	Treatment arm

Arm description:

1.2 mg dose of vafidemstat five times in week (fiw).

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:

Vafidemstat was administered daily for 5 days, at a dose of 1.2 mg/day.

Number of subjects in period 1[1]	Treatment arm
Started	12
Completed	7
Not completed	5
Adverse event, serious fatal	1
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 12 subjects were enrolled however 5 did not complet the study treatment period due to the reasons described.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment arm
Reporting group description:	
1.2 mg dose of vafidemstat five times in week (fiw).	

Reporting group values	Treatment arm	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1	1	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	74.83		
standard deviation	± 7.18	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	5	5	

End points

End points reporting groups

Reporting group title	Treatment arm
Reporting group description:	
1.2 mg dose of vafidemstat five times in week (fiw).	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population includes all patients who received at least one dose of the study IMP	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients who received at least one dose of the IMP and have completed at least one of the primary endpoints (NPI-A/A, CMAI, CGI-A/A) in Baseline Visit (Week 1-Day 1) and any other post-Baseline Visit.	
Subject analysis set title	PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-Protocol Set 1 (PPS) until Visit 4: All randomized patients of the FAS who have completed the assessment of at least one primary endpoint (NPI-A/A, CMAI, CGI-A/A) at Visit 4 (Week 8), and who were deemed to have no major protocol violations until Week 24 that could interfere with the objectives of this study. This is a subpopulation of the FAS.	
Subject analysis set title	PPS2
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-Protocol Set 2 (PPS2) until Visit 8: All randomized patients of the FAS who have completed the assessment of at least one primary endpoint (NPI-A/A, CMAI, CGI-A/A) at Visit 8 (Week 24), and who were deemed to have no major protocol violations until Week 24 that could interfere with the objectives of this study. This is a subpopulation of the FAS. Two subjects continued the study treatment for an additional 24-weeks, for a total of up to 48 weeks.	

Primary: Change from baseline in NPI-4 A/A

End point title	Change from baseline in NPI-4 A/A[1]
End point description:	
End point type	Primary
End point timeframe:	
From baseline to week 8 and to week 24	

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: It is a single-arm study, comparisons were made within that single-arm comparing baseline and end-of-treatment data.

End point values	FAS	PPS	PPS2	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	10	7	
Units: Subscale scores				
arithmetic mean (standard deviation)				
NPI-A/A Subscale scores	12.17 (± 6.25)	6.5 (± 4.65)	2.29 (± 3.40)	

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in the Cohen-Mansfield Agitation inventory (CMAI)

End point title	Change from baseline in the Cohen-Mansfield Agitation inventory (CMAI)[2]

End point description:

End point type	Primary

End point timeframe:

From baseline to week 8 and to week 24

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: It is a single-arm study, comparisons were made within that single-arm comparing baseline and end-of-treatment data.

End point values	FAS	PPS	PPS2	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	10	7	
Units: CMAI score				
arithmetic mean (standard deviation)				
CMAI score	54.58 (± 14.58)	52.50 (± 11.17)	39.29 (± 6.45)	

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in the Clinical Global Impression – Improvement Agitation/Aggression (CGI- I A/A)

End point title	Change from baseline in the Clinical Global Impression – Improvement Agitation/Aggression (CGI- I A/A)[3]

End point description:

End point type	Primary

End point timeframe:

From baseline to week 8 and to week 24

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: It is a single-arm study, comparisons were made within that single-arm comparing baseline and end-of-treatment data.

End point values	FAS	PPS	PPS2	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	10	7	
Units: CGI-I A/A score				
arithmetic mean (standard deviation)				
CGI-I-A/A	4.00 (± 0.00)	3.60 (± 1.78)	1.86 (± 0.90)	

Statistical analyses

No statistical analyses for this end point

Primary: Change over time in the CGI- I A/A

End point title	Change over time in the CGI- I A/A[4]

End point description:

End point type	Primary

End point timeframe:

From baseline to week 8 and to week 24

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: It is a single-arm study, comparisons were made within that single-arm comparing baseline and end-of-treatment data.

End point values	PPS	PPS2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[5]	7[6]		
Units: CGI- I A/A score				
arithmetic mean (standard deviation)				
CGI-I-A/A score (absolute change)	-0.40 (± 1.78)	-2.14 (± 0.90)		

Notes:

[5] - Change: Visit 4 - Visit 1 (week 8 - week 1)

[6] - Change: Visit 8 - Visit 1 (week 24 - week 1)

Statistical analyses

No statistical analyses for this end point

Primary: Change over time in the NPI-4 A/A

End point title	Change over time in the NPI-4 A/A[7]

End point description:

End point type	Primary

End point timeframe:

From baseline to week 8 and to week 24

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: It is a single-arm study, comparisons were made within that single-arm comparing baseline and end-of-treatment data.

End point values	PPS	PPS2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[8]	7[9]		
Units: Subscale score				
arithmetic mean (standard deviation)				
NPI-A/A Subscale score	-4.00 (± 8.01)	-9.71 (± 5.85)		

Notes:

[8] - Change: Visit 4 - Visit 1 (week 8 - week 1)

[9] - Change: Visit 8 - Visit 1 (week 24 - week 1)

Statistical analyses

No statistical analyses for this end point

Primary: Change over time in the CMAI

End point title	Change over time in the CMAI[10]

End point description:

End point type	Primary

End point timeframe:

From baseline to week 8 and to week 24

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a single-arm study, comparisons were made within that single-arm comparing baseline and end-of-treatment data.

End point values	PPS	PPS2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[11]	7[12]		
Units: CMAI score				
arithmetic mean (standard deviation)				
Total CMAI score (absolute change)	-0.7 (± 16.63)	-16.71 (± 17.58)		

Notes:

[11] - Change: Visit 4 - Visit 1 (week 8 - week 1)

[12] - Change: Visit 8 - Visit 1 (week 24 - week 1)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24-week treatment period	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0
Reporting groups	
Reporting group title	Treatment arm
Reporting group description: 1.2 mg dose of vafidemstat five times in week (fiw).	

Serious adverse events	Treatment arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Treatment arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 12 (75.00%)		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood creatine increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hematocrit decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Protein C increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Edema peripheral			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			

Behaviour disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rotator cuff syndrome			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Oral infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Iron deficiency			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2019	Protocol v2.0: Extended-treatment period
30 January 2020	Protocol v3.0: Extended-treatment period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Small sample size and open study design. A larger, randomized, double-blind, placebo-controlled trial is needed to confirm study results and demonstrate vafidemstat’s potential efficacy in treating agitation and aggression in moderate-to-severe AD.

Notes: