Clinical trial results:
A multicenter, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of lucerastat oral monotherapy in adult subjects with Fabry disease.

Summary

EudraCT number	2017-003369-85
Trial protocol	GB AT NL BE IE ES NO IT
Global end of trial date	02 September 2021

Results information

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

Trial information

Trial identification

Sponsor protocol code	ID-069A301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03425539
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Idorsia Pharmaceuticals Ltd
Sponsor organisation address	Hegenheimermattweg 91, Allschwil, Switzerland, 4123
Public contact	Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com
Scientific contact	Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To determine the effect of lucerastat on neuropathic pain in subjects with Fabry disease (FD).

Protection of trial subjects:

The protocol and any material provided to the subject (such as a subject information sheet or description of the study used to obtain informed consent) were reviewed and approved by the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB) before the study was started.
Sponsor personnel and the investigators ensured that the study was conducted in full compliance with ICH-GCP guidelines, the principles of the "Declaration of Helsinki", and with the laws and regulations of the countries in which the study was conducted.
Both the sponsor and the investigator had the right to terminate the study at any time, and in such a case, were responsible for protecting the subjects' interests. The investigator was responsible for maintaining the subjects' identities in strictest confidence.
Prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study, written informed consent was obtained from each participating subject. It was made clear to each subject that he or she was completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 May 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 11

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 4
Worldwide total number of subjects	118
EEA total number of subjects	50

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)	111
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 49 sites in 14 countries, including North America (USA, CAN), Europe (Austria, Belgium, Germany, Ireland, Italy, Netherlands, Norway, Poland, Spain, Switzerland, UK), and Australia.

Pre-assignment

Screening details:

Screening period: From signing informed consent to the day before subject randomization (6 to 7 weeks duration).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lucerastat

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Lucerastat
Investigational medicinal product code	ACT-434964
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lucerastat (ACT-434964) was provided as hard-gelatin capsules containing 250 mg of lucerastat. Capsules were administered orally b.i.d. to provide a lucerastat dose of 250, 500, 750, or 1000 mg b.i.d. based on the subject’s eGFR.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Matching placebo capsules were administered orally b.i.d., with the number of capsules administered based on the subject’s eGFR.

Number of subjects in period 1	Lucerastat	Placebo
Started	80	38
Completed	75	34
Not completed	5	4
Consent withdrawn by subject	3	-
Adverse event, non-fatal	2	2
Randomized but not treated	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Lucerastat
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Lucerastat	Placebo	Total
Number of subjects	80	38	118
Age categorical Units: Subjects			
Adults (18-64 years)	74	37	111
From 65-84 years	6	1	7
Age continuous Units: years			
median	38	39	
full range (min-max)	18 to 74	18 to 65	-
Gender categorical Units: Subjects			
Female	43	20	63
Male	37	18	55

End points

End points reporting groups

Reporting group title	Lucerastat
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Neuropathic pain monthly score (modified BPI-SF3): Change from baseline to Month 6

End point title	Neuropathic pain monthly score (modified BPI-SF3): Change from baseline to Month 6
End point description:	
End point type	Primary
End point timeframe: From baseline to Month 6	

End point values	Lucerastat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	37		
Units: Score				
least squares mean (confidence interval 95%)	-1.64 (-2.11 to -1.16)	-2.05 (-2.73 to -1.37)		

Statistical analyses

Statistical analysis title	Neuropathic pain monthly score: ANCOVA
Statistical analysis description: Neuropathic pain monthly score (modified BPI-SF3): main analysis of change from baseline to Month 6 (ANCOVA)	
Comparison groups	Lucerastat v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.3189
Method	ANCOVA
Parameter estimate	LS Mean difference vs. placebo
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.23

Notes:

[1] - An ANCOVA was applied to the change from baseline to Month 6 including the terms baseline value, the two stratification factors (sex and ERT treatment status), and the treatment group.

Secondary: Plasma Gb3 (ng/ml): Change from baseline to Month 6

End point title	Plasma Gb3 (ng/ml): Change from baseline to Month 6

End point description:

End point type	Secondary

End point timeframe:

From baseline to Month 6

End point values	Lucerastat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	37		
Units: ng/ml				
least squares mean (confidence interval 95%)	-672.68 (-798.91 to -546.46)	200.84 (14.29 to 387.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Abdominal pain monthly score: Change from baseline to Month 6

End point title	Abdominal pain monthly score: Change from baseline to Month 6

End point description:

From baseline to Month 6

End point type	Secondary

End point timeframe:

From baseline to Month 6

End point values	Lucerastat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	29		
Units: Score				
least squares mean (confidence interval 95%)	-1.37 (-1.86 to -0.87)	-1.68 (-2.38 to -0.98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with diarrhea: Change from baseline to Month 6

End point title	Number of days with diarrhea: Change from baseline to Month 6

End point description:

End point type	Secondary

End point timeframe:

From baseline to Month 6

End point values	Lucerastat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Number of days				
arithmetic mean (standard deviation)	-3.45 (± 4.96)	-3.95 (± 9.29)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events from the treatment period are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Lucerastat

Reporting group description:

Lucerastat

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Lucerastat	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 80 (6.25%)	1 / 37 (2.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Implantable defibrillator insertion			
subjects affected / exposed	1 / 80 (1.25%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 80 (1.25%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug withdrawal syndrome			

subjects affected / exposed	1 / 80 (1.25%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 80 (1.25%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 80 (1.25%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Hepatitis viral			
subjects affected / exposed	1 / 80 (1.25%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 80 (1.25%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic encephalopathy			
subjects affected / exposed	1 / 80 (1.25%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 80 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lucerastat	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 80 (57.50%)	21 / 37 (56.76%)	
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 80 (0.00%)	4 / 37 (10.81%)	
occurrences (all)	0	4	
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	5 / 80 (6.25%)	1 / 37 (2.70%)	
occurrences (all)	10	1	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 80 (11.25%)	4 / 37 (10.81%)	
occurrences (all)	11	4	
Neuralgia			
subjects affected / exposed	6 / 80 (7.50%)	3 / 37 (8.11%)	
occurrences (all)	6	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 80 (3.75%)	6 / 37 (16.22%)	
occurrences (all)	3	7	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 80 (1.25%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 80 (1.25%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Abdominal distension			

subjects affected / exposed	4 / 80 (5.00%)	4 / 37 (10.81%)	
occurrences (all)	4	4	
Abdominal pain			
subjects affected / exposed	4 / 80 (5.00%)	1 / 37 (2.70%)	
occurrences (all)	5	2	
Diarrhoea			
subjects affected / exposed	9 / 80 (11.25%)	1 / 37 (2.70%)	
occurrences (all)	10	1	
Dry mouth			
subjects affected / exposed	4 / 80 (5.00%)	1 / 37 (2.70%)	
occurrences (all)	4	1	
Flatulence			
subjects affected / exposed	7 / 80 (8.75%)	1 / 37 (2.70%)	
occurrences (all)	7	1	
Nausea			
subjects affected / exposed	11 / 80 (13.75%)	1 / 37 (2.70%)	
occurrences (all)	13	1	
Vomiting			
subjects affected / exposed	6 / 80 (7.50%)	0 / 37 (0.00%)	
occurrences (all)	7	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 80 (7.50%)	0 / 37 (0.00%)	
occurrences (all)	6	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 80 (6.25%)	0 / 37 (0.00%)	
occurrences (all)	5	0	
Back pain			
subjects affected / exposed	5 / 80 (6.25%)	2 / 37 (5.41%)	
occurrences (all)	5	2	
Muscle spasms			
subjects affected / exposed	2 / 80 (2.50%)	2 / 37 (5.41%)	
occurrences (all)	4	3	
Infections and infestations			

COVID-19			
subjects affected / exposed	2 / 80 (2.50%)	2 / 37 (5.41%)	
occurrences (all)	2	2	
Lower respiratory tract infection			
subjects affected / exposed	0 / 80 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	8 / 80 (10.00%)	5 / 37 (13.51%)	
occurrences (all)	10	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2018	1. The definition of neuropathic pain was split to improve readability and subject comprehension. The descriptor "numbness" was removed from the description as it was considered to be a distinct concept that does not necessarily describe neuropathic pain severity. The concept of intermittence was also added to the definition of neuropathic pain. 2. A new Patient Global Impression of Severity scale was added to assess the overall severity of neuropathic pain. 3. It was clarified that current guidelines for the diagnosis and treatment of FD were to be followed. 4. A more explicit definition of the global end of the study was included. 5. The process of eDiary data availability, transfer, encoding, and the measures taken to maintain privacy of the subject were clarified. 6. Exclusion criteria were adjusted to emphasize that any subject at high risk of developing clinical signs of organ involvement within the time period of the study, as per investigator judgment would be excluded from the study.
25 October 2018	The results of a clinical drug-drug interaction (DDI) study (ID-069-105) with the organic cation transporter 2 (OCT2) inhibitor cimetidine led to the conclusion that lucerastat can be administered concomitantly with OCT2 inhibitors without need for dose adaptation. Therefore, respective protocol restrictions at study entry (exclusion criterion #15) and during the study (forbidden concomitant therapy) related to the use of OCT2 inhibitors have been removed.
01 October 2020	The main reason for the amendment was to change the methodology used to analyze the primary endpoint from a dichotomous responder analysis, based on a reduction of at least 30% from baseline to Month 6 in modified BPI-SF3 score, to an analysis of the change from baseline to Month 6 in modified BPI-SF3 score. Analyzing the primary endpoint as a continuous variable avoided a loss in information caused by the dichotomization of the endpoint variable. It required fewer subjects to maintain the statistical power to detect a difference between lucerastat and placebo. With the proposed continuous analysis, 99 subjects are required to achieve a power of 87.2%, which is comparable to the power in the range of 81.984.1% for the current responder analysis based on 108 subjects. The dichotomous responder analysis was documented to support and establish clinical relevance. This change was agreed with the FDA in order to help overcome challenges in recruitment of subjects with a rare disease in the context of the COVID 19 pandemic and complete the study. The change was restricted to the primary statistical analysis and did not alter the study population or the study's primary objective.
24 August 2021	The main purpose of the amendment was to change the statistical method used to analyze the secondary endpoint "Change from baseline to Month 6 in the number of days with at least 1 stool of a BSS consistency Type 6 or 7", from a parametric analysis (assuming normality) to a non-parametric analysis. This change in analysis was warranted because the blinded baseline data review suggested that the endpoint was not normally distributed. The necessity to make a change to this analysis method was discussed with the FDA; the change is restricted to the statistical analysis of the last secondary endpoint in the testing strategy and does not alter the study population and the primary and secondary objectives of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported