Clinical trial results:
A Randomized, Double-Blind, Delayed-Start Study of LY3314814 (AZD3293) in Early Alzheimer's Disease Dementia (Extension of Study AZES, The AMARANTH Study)

Summary

EudraCT number	2016-003440-36
Trial protocol	HU DE PL ES BE GB FR IT RO
Global end of trial date	02 October 2018

Results information

Result version number	v2 (current)
This version publication date	05 January 2020
First version publication date	27 June 2019
Version creation reason	• Correction of full data set Revision to Full Data Set

Trial information

Trial identification

Sponsor protocol code	I8D-MC-AZFD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02972658
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16557

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,
Sponsor organisation name	AstraZeneca UK Limited
Sponsor organisation address	Charter Way, Macclesfield, Cheshire, United Kingdom, SK10 2NA
Public contact	Available Mon Fri 9 AM 5 PM EST, AstraZeneca UK Limited, 44 1625-58-2828,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, AstraZeneca UK Limited, 44 1625-58-2828,

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	02 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study is an extension of study I8D-MC-AZES (NCT02245737), the AMARANTH study. The purpose of this study is to evaluate the effectiveness of the study drug lanabecestat in participants with early Alzheimer's disease dementia at the time of entry into study I8D-MC-AZES.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2017
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	Puerto Rico: 1
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	United States: 94
Country: Number of subjects enrolled	Japan: 39
Country: Number of subjects enrolled	United Kingdom: 46
Country: Number of subjects enrolled	Spain: 60
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	Germany: 24

Worldwide total number of subjects	421
EEA total number of subjects	211

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)	96
From 65 to 84 years	325
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who completed feeder study (AZES (NCT02245737)) were enrolled in this study.

Pre-assignment

Screening details:

Participants who were randomized in Study AZES to either 20 mg or 50 mg of lanabecestat continued on the treatment allocation from the feeder study. Participants randomized to placebo in Study AZES were randomized in a blinded fashion, 1:1 ratio, to either lanabecestat 20 mg or 50 mg daily (QD), administered orally.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	AZES Placebo/AZFD Lanabecestat 20 mg

Arm description:

Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 20 mg.

Arm type	Experimental
Investigational medicinal product name	Lanabecestat
Investigational medicinal product code	
Other name	LY3314814, AZD3293
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

20 mg film-coated tablets of lanabecestat administered orally once a day.

Arm title	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg

Arm description:

Participants who received lanabecestat 20 mg in the feeder study (AZES) were randomized to receive lanabecestat 20 mg. 1 participant was incorrectly marked as "Completed" rather than study terminated by Sponsor.

Arm type	Experimental
Investigational medicinal product name	Lanabecestat
Investigational medicinal product code	
Other name	LY3314814, AZD3293
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

20 mg film-coated tablets of lanabecestat administered orally once a day.

Arm title	AZES Placebo/AZFD Lanabecestat 50 mg

Arm description:

Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.

Arm type	Experimental

Investigational medicinal product name	Lanabecestat
Investigational medicinal product code	
Other name	LY3314814, AZD3293
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg film-coated tablets of lanabecestat administered orally once a day.

Arm title	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg

Arm description:

Participants who received lanabecestat 50 mg in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.

Arm type	Experimental
Investigational medicinal product name	Lanabecestat
Investigational medicinal product code	
Other name	LY3314814, AZD3293
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg film-coated tablets of lanabecestat administered orally once a day.

Number of subjects in period 1	AZES Placebo/AZFD Lanabecestat 20 mg	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg	AZES Placebo/AZFD Lanabecestat 50 mg
Started	76	139	75
Received at least 1 Dose of Study drug	76	139	74
Completed	0	1	0
Not completed	76	138	75
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	4	4	1
Other-selected by Investigator	1	1	-
Withdrawal due to Caregiver Circumstance	1	1	1
Adverse event, non-fatal	-	3	-
Progressive Disease	-	1	-
Sponsor Decision	70	127	72
Lost to follow-up	-	1	1

Number of subjects in period 1	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg
Started	131
Received at least 1 Dose of Study drug	131
Completed	0
Not completed	131
Adverse event, serious fatal	1
Consent withdrawn by subject	6

Other-selected by Investigator	-
Withdrawal due to Caregiver Circumstance	-
Adverse event, non-fatal	2
Progressive Disease	1
Sponsor Decision	119
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	AZES Placebo/AZFD Lanabecestat 20 mg
Reporting group description:	
Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 20 mg.	
Reporting group title	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg
Reporting group description:	
Participants who received lanabecestat 20 mg in the feeder study (AZES) were randomized to receive lanabecestat 20 mg. 1 participant was incorrectly marked as "Completed" rather than study terminated by Sponsor.	
Reporting group title	AZES Placebo/AZFD Lanabecestat 50 mg
Reporting group description:	
Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.	
Reporting group title	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg
Reporting group description:	
Participants who received lanabecestat 50 mg in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.	

Reporting group values	AZES Placebo/AZFD Lanabecestat 20 mg	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg	AZES Placebo/AZFD Lanabecestat 50 mg
Number of subjects	76	139	75
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			
Details are from AZES baseline.			
Units: years			
arithmetic mean	70.7	69.8	71.1
standard deviation	± 6.6	± 7.8	± 6.6
Gender categorical			
Units: Subjects			
Female	35	76	40
Male	41	63	35
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	7	4	4
Not Hispanic or Latino	62	115	54
Unknown or Not Reported	7	20	17

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	7	23	10
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	1
White	64	104	51
More than one race	0	0	0
Unknown or Not Reported	5	10	13
Region of Enrollment Units: Subjects			
Puerto Rico	0	1	0
Romania	1	1	0
Hungary	1	0	0
United States	23	35	13
Japan	6	14	5
United Kingdom	8	17	8
Spain	10	21	8
Canada	6	8	5
South Korea	1	7	3
Belgium	5	2	0
Poland	6	8	6
France	4	9	12
Australia	3	13	8
Germany	2	3	7
ADAS-Cog13 (13-item Alzheimer's Disease Assessment Scale)			
ADAS-Cog13, a 13-item rating scale, measured the severity of cognitive dysfunction in persons with Alzheimer's disease (AD). Scores ranged from 0 to 85, with a higher score indicating worse cognitive functioning. Details are from AZES baseline.			
Units: Units on a Scale			
arithmetic mean	27.9	29.6	27.0
standard deviation	± 8.3	± 7.8	± 7.5

Reporting group values	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg	Total	
Number of subjects	131	421	
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			
Details are from AZES baseline.			
Units: years			
arithmetic mean	70.1		
standard deviation	± 6.7	-	
Gender categorical			
Units: Subjects			
Female	75	226	
Male	56	195	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	18	
Not Hispanic or Latino	114	345	
Unknown or Not Reported	14	58	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	16	56	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	3	
White	106	325	
More than one race	0	0	
Unknown or Not Reported	9	37	
Region of Enrollment			
Units: Subjects			
Puerto Rico	0	1	
Romania	0	2	
Hungary	0	1	
United States	23	94	
Japan	14	39	
United Kingdom	13	46	
Spain	21	60	
Canada	14	33	
South Korea	2	13	
Belgium	4	11	
Poland	14	34	
France	8	33	
Australia	6	30	
Germany	12	24	
ADAS-Cog13 (13-item Alzheimer’s Disease Assessment Scale)			
ADAS-Cog13, a 13-item rating scale, measured the severity of cognitive dysfunction in persons with Alzheimer's disease (AD). Scores ranged from 0 to 85, with a higher score indicating worse cognitive functioning. Details are from AZES baseline.			
Units: Units on a Scale			
arithmetic mean	27.1		
standard deviation	± 7.5	-	

End points

End points reporting groups

Reporting group title	AZES Placebo/AZFD Lanabecestat 20 mg
Reporting group description:	
Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 20 mg.	
Reporting group title	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg
Reporting group description:	
Participants who received lanabecestat 20 mg in the feeder study (AZES) were randomized to receive lanabecestat 20 mg. 1 participant was incorrectly marked as "Completed" rather than study terminated by Sponsor.	
Reporting group title	AZES Placebo/AZFD Lanabecestat 50 mg
Reporting group description:	
Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.	
Reporting group title	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg
Reporting group description:	
Participants who received lanabecestat 50 mg in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.	

Primary: Change From Baseline Analysis on the 13-item Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog13)

End point title	Change From Baseline Analysis on the 13-item Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog13)[1]
End point description:	
ADAS-Cog13 is a psychometric instrument that evaluates word recall, ability to follow commands, constructional praxis, naming, ideational praxis, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure of delayed word recall and concentration/ distractibility. The total score of the 13-item scale ranges from 0 to 85, with an increase in score indicating cognitive worsening. Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with factors for treatment, visit, treatment*visit, baseline efficacy score, baseline efficacy score-by-visit interaction, disease status at baseline, APOE4 (apolipoprotein E4) status, AChEI (acetylcholinesterase inhibitor) use at baseline, age at baseline, and pooled country. Analysis Population Description (APD): All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for ADAS-Cog13 measure.	
End point type	Primary
End point timeframe:	
AZES Baseline through AZFD Week 26	

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: Because the feeder study AZES was stopped for futility, the original primary efficacy analysis (Delayed Start analysis) was replaced with MMRM analysis across AZES and AZFD. No comparisons between treatment groups were made.

End point values	AZES Placebo/AZFD Lanabecestat 20 mg	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg	AZES Placebo/AZFD Lanabecestat 50 mg	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	139	75	131
Units: Units on a scale				
least squares mean (standard error)	9.61 (± 1.60)	9.25 (± 1.21)	8.41 (± 1.65)	10.41 (± 1.25)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Delayed Start Analysis on the Alzheimer´s Disease Cooperative Study Activities of Daily Living Inventory Instrumental Items (ADCS-iADL)

End point title	Change From Baseline in Delayed Start Analysis on the Alzheimer´s Disease Cooperative Study Activities of Daily Living Inventory Instrumental Items (ADCS-iADL)

End point description:

The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire answered by the participant's caregiver. The ADCS-ADL measures both basic and instrumental activities of daily living by participants. The range for the ADCS-iADL is 0-59 with higher scores reflecting better performance. LS Mean was determined by MMRM with factors for treatment, visit, treatment*visit, baseline efficacy score, baseline efficacy score-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, age at baseline, and pooled country.
APD: All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for ADCS-iADL measure.

End point type	Secondary

End point timeframe:

AZES Baseline through AZFD Week 26

End point values	AZES Placebo/AZFD Lanabecestat 20 mg	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg	AZES Placebo/AZFD Lanabecestat 50 mg	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	139	74	129
Units: Units on a scale				
least squares mean (standard error)	-9.19 (± 1.47)	-8.45 (± 1.10)	-7.37 (± 1.51)	-7.48 (± 1.14)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Delayed Start Analysis on the Functional Activities Questionnaire (FAQ) Score

End point title	Change From Baseline in Delayed Start Analysis on the Functional Activities Questionnaire (FAQ) Score

End point description:

FAQ is a 10-item, caregiver-questionnaire and was administered to the study partner and asked to rate the participant's ability to perform a variety of activities ranging from writing checks, assembling tax records, shopping, playing games, food preparation, traveling, keeping appointments, traveling out of

neighborhood, keeping track of current events and understanding media. FAQ total score was calculated by adding the scores from each of the 10 items. Each activity is rated on a scale from 0 to 3 (Never did and would have difficulty now =1; Never did but could do now =0; Normal =0; Has difficulty but does by self =1; Requires assistance =2; Dependent =3). FAQ scale is 0 to 30, with higher scores indicating greater impairment. LS Mean was determined by MMRM.
APD: All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for FAQ score.

End point type	Secondary

End point timeframe:

AZES Baseline through AZFD Week 26

End point values	AZES Placebo/AZFD Lanabecestat 20 mg	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg	AZES Placebo/AZFD Lanabecestat 50 mg	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	137	74	130
Units: Units on a scale				
least squares mean (standard error)	6.28 (± 0.98)	7.09 (± 0.76)	6.73 (± 1.01)	6.91 (± 0.79)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Delayed Start Analysis on the Integrated Alzheimer's Disease Rating Scale (iADRS) Score

End point title	Change From Baseline in Delayed Start Analysis on the Integrated Alzheimer's Disease Rating Scale (iADRS) Score

End point description:

The iADRS is a composite that measures both cognition and function. The iADRS comprises scores form the ADAS- Cog and the ADCS-iADL. The iADRS is calculated as a linear combination of the total scores of the ADAS-Cog13 (score range 0 to 85 with higher scores reflecting worse performance) and the ADCS-iADL (score range from 0-59 with higher scores reflecting better performance). The iADRS score ranges from 0 to 144 with with higher scores indicating greater impairment. LS Mean was determined by MMRM with factors for treatment, visit, treatment*visit, baseline efficacy score, baseline efficacy score-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, age at baseline, and pooled country.
APD: All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for iADRS.

End point type	Secondary

End point timeframe:

AZES Baseline through AZFD Week 26

End point values	AZES Placebo/AZFD Lanabecestat 20 mg	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg	AZES Placebo/AZFD Lanabecestat 50 mg	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	138	72	123
Units: Units on a scale				
least squares mean (standard error)	-18.85 (± 2.58)	-17.57 (± 1.97)	-15.37 (± 2.76)	-18.37 (± 2.09)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Delayed Start Analysis on the Mini-Mental Status Examination (MMSE)

End point title	Change From Baseline in Delayed Start Analysis on the Mini-Mental Status Examination (MMSE)

End point description:

The MMSE is an instrument used to assess a participant's cognitive function. The MMSE assesses orientation to time and place, immediate and delayed recall of words, attention and calculation, language (naming, comprehension and repetition), and spatial ability (copying a figure). The range for MMSE total Score is 0 to 30, with a higher score indicating better cognitive performance. LS Mean was determined by MMRM methodology with factors for treatment, visit, treatment*visit, baseline efficacy score, baseline efficacy score-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, age at baseline, and pooled country.
APD: All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for MMSE.

End point type	Secondary

End point timeframe:

AZES Baseline through AZFD Week 26

End point values	AZES Placebo/AZFD Lanabecestat 20 mg	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg	AZES Placebo/AZFD Lanabecestat 50 mg	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	139	75	131
Units: Units on a scale				
least squares mean (standard error)	-5.84 (± 0.71)	-5.73 (± 0.54)	-4.72 (± 0.72)	-5.25 (± 0.56)

Statistical analyses

No statistical analyses for this end point

Secondary: Delayed Start Analysis on the ADAS-Cog13

End point title	Delayed Start Analysis on the ADAS-Cog13

End point description:

ADAS-Cog13 (13-item version of ADAS Cog) is a psychometric instrument that evaluates word recall, ability to follow commands, constructional praxis, naming, ideational praxis, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure of delayed word recall and concentration/ distractibility. The total score of the 13-item scale ranges from 0 to 85, with an increase in score indicating cognitive worsening. Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with factors for treatment, visit, treatment*visit, baseline efficacy score, baseline efficacy score-by-visit interaction, disease status at baseline, APOE4 (apolipoprotein E4) status, AChEI (acetylcholinesterase inhibitor) use at baseline, age at baseline, and pooled country.
APD: All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for ADAS-Cog13 measure.

End point type	Secondary

End point timeframe:

AZES Baseline through AZFD Week 52

End point values	AZES Placebo/AZFD Lanabecestat 20 mg	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg	AZES Placebo/AZFD Lanabecestat 50 mg	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	139	75	131
Units: Units on a scale				
least squares mean (standard error)	16.64 (± 3.45)	12.40 (± 2.25)	16.79 (± 2.47)	15.05 (± 2.06)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up To 156 Weeks	
Adverse event reporting additional description:	
All AZFD participants who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg
Reporting group description:	
Participants who received Lanabecestat 20 mg in the feeder study (AZES) received Lanabecestat 20 mg in AZFD.	
Reporting group title	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg
Reporting group description:	
Participants who received Lanabecestat 50 mg in the feeder study (AZES) received Lanabecestat 50 mg in AZFD.	
Reporting group title	AZES Placebo/AZFD Lanabecestat 20 mg
Reporting group description:	
Participants who received placebo in the feeder study (AZES) received Lanabecestat 20 mg in AZFD.	
Reporting group title	AZES Placebo/AZFD Lanabecestat 50 mg
Reporting group description:	
Participants who received placebo in the feeder study (AZES) received Lanabecestat 50 mg in AZFD.	

Serious adverse events	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg	AZES Placebo/AZFD Lanabecestat 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 139 (5.76%)	7 / 131 (5.34%)	3 / 76 (3.95%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
breast cancer in situ			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 139 (0.72%)	0 / 131 (0.00%)	0 / 76 (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
breast cancer metastatic			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 139 (0.72%)	0 / 131 (0.00%)	0 / 76 (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
laryngeal squamous cell carcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	0 / 131 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
electrocardiogram repolarisation abnormality			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	0 / 131 (0.00%)	0 / 76 (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
weight decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	1 / 131 (0.76%)	0 / 76 (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
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	1 / 131 (0.76%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
femoral neck fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 139 (0.72%)	0 / 131 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
femur fracture			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 139 (0.00%)	1 / 131 (0.76%)	0 / 76 (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
radiation proctitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	0 / 131 (0.00%)	0 / 76 (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			
bradycardia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	1 / 131 (0.76%)	0 / 76 (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			
ischaemic stroke			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 139 (0.72%)	0 / 131 (0.00%)	0 / 76 (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
optic neuritis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 139 (0.72%)	0 / 131 (0.00%)	0 / 76 (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
Gastrointestinal disorders			
colitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 139 (0.72%)	0 / 131 (0.00%)	0 / 76 (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
enteritis			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 139 (0.72%)	0 / 131 (0.00%)	0 / 76 (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
oesophageal motility disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	1 / 131 (0.76%)	0 / 76 (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
small intestinal obstruction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	0 / 131 (0.00%)	0 / 76 (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			
depression			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 139 (0.72%)	0 / 131 (0.00%)	0 / 76 (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
neuropsychiatric symptoms			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	1 / 131 (0.76%)	0 / 76 (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
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	1 / 131 (0.76%)	0 / 76 (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
musculoskeletal chest pain			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 139 (0.00%)	1 / 131 (0.76%)	0 / 76 (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
Infections and infestations			
diverticulitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	1 / 131 (0.76%)	0 / 76 (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
influenza			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	0 / 131 (0.00%)	0 / 76 (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			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 139 (0.00%)	1 / 131 (0.76%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Serious adverse events	AZES Placebo/AZFD Lanabecestat 50 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 74 (6.76%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
breast cancer in situ			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
breast cancer metastatic			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
laryngeal squamous cell carcinoma				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
electrocardiogram repolarisation abnormality				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
weight decreased				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
fall				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
femoral neck fracture				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
femur fracture				
alternative dictionary used: MedDRA 21.1				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
radiation proctitis				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
bradycardia				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
ischaemic stroke				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
optic neuritis				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
colitis				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
enteritis				
alternative dictionary used: MedDRA 21.1				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
oesophageal motility disorder				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
small intestinal obstruction				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
depression				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
neuropsychiatric symptoms				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
back pain				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
musculoskeletal chest pain				
alternative dictionary used: MedDRA 21.1				

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
diverticulitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
influenza			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pneumonia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 74 (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: 5 %

Non-serious adverse events	AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg	AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg	AZES Placebo/AZFD Lanabecestat 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 139 (16.55%)	17 / 131 (12.98%)	11 / 76 (14.47%)
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	7 / 139 (5.04%)	5 / 131 (3.82%)	4 / 76 (5.26%)
occurrences (all)	8	8	4
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	8 / 139 (5.76%)	6 / 131 (4.58%)	2 / 76 (2.63%)
occurrences (all)	8	6	2
Psychiatric disorders			
depression			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 139 (2.16%)	2 / 131 (1.53%)	4 / 76 (5.26%)
occurrences (all)	3	2	4
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	8 / 139 (5.76%)	5 / 131 (3.82%)	1 / 76 (1.32%)
occurrences (all)	10	7	1

Non-serious adverse events	AZES Placebo/AZFD Lanabecestat 50 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 74 (10.81%)		
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences (all)	2		
Psychiatric disorders			
depression			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 February 2018	Amendment (a): Amended to -Extend the study additional year from original protocol. -Provided Clarification of when temporary discontinuation would be considered due to vasogenic edema.

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.

This study was stopped after an independent assessment concluded that the feeder study AZES was futile. Because of this, the originally planned delayed-start analysis for this study was not performed.

Notes: