Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled and Delayed-Start Study of LY3314814 in Mild Alzheimer's Disease Dementia (The DAYBREAK Study)

Summary

EudraCT number	2015-005625-39
Trial protocol	GB PT ES PL CZ DK NL FR IT
Global end of trial date	28 September 2018

Results information

Result version number	v1
This version publication date	27 June 2019
First version publication date	27 June 2019

Trial information

Trial identification

Sponsor protocol code	I8D-MC-AZET

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02783573
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16024

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	28 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the efficacy of the study drug known as lanabecestat in participants with mild Alzheimer's disease (AD) dementia.

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	01 July 2016
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	Czech Republic: 129
Country: Number of subjects enrolled	United States: 600
Country: Number of subjects enrolled	Japan: 119
Country: Number of subjects enrolled	United Kingdom: 68
Country: Number of subjects enrolled	Portugal: 24
Country: Number of subjects enrolled	Russian Federation: 100
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	Canada: 96
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Netherlands: 30
Country: Number of subjects enrolled	China: 2
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	Poland: 122
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	Italy: 66
Country: Number of subjects enrolled	Mexico: 29
Country: Number of subjects enrolled	France: 93
Country: Number of subjects enrolled	Germany: 60

Worldwide total number of subjects	1722
EEA total number of subjects	693

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)	257
From 65 to 84 years	1435
85 years and over	30

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

No Text Available

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo film-coated oral tablets once daily.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated tablets of placebo administered orally once a day.

Arm title	Lanabecestat 20 mg

Arm description:

Participants received lanabecestat 20 mg film-coated oral tablets once daily.

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	Lanabecestat 50 mg

Arm description:

Participants received lanabecestat 50 mg film-coated oral tablets once daily.

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	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg
Started	562	590	570
Completed	26	28	22
Not completed	536	562	548
Adverse event, serious fatal	4	2	3
Physician decision	3	1	3
Consent withdrawn by subject	15	20	23
Non-Compliance	-	1	-
Adverse event, non-fatal	13	17	13
Withdrawal due to Caregiver Circumstance	3	3	9
Other-selected by Investigator	-	1	2
Sponsor Decision	494	512	492
Lost to follow-up	3	3	1
Protocol deviation	1	2	-
Lack of efficacy	-	-	2

Period 2

Period 2 title	Delayed-Start Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Lanabecestat 20 mg

Arm description:
Participants received lanabecestat 20 mg film-coated oral tablets once daily.

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.

Arm title	Lanabecestat 50 mg

Arm description:

Participants received lanabecestat 50 mg film-coated oral tablets once daily.

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.

Number of subjects in period 2[1]	Lanabecestat 20 mg	Lanabecestat 50 mg
Started	17	12
Completed	0	0
Not completed	17	12
Sponsor Decision	17	12

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: Patients who completed period 1 may not have entered period 2 due to early termination of the study.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo film-coated oral tablets once daily.	
Reporting group title	Lanabecestat 20 mg
Reporting group description:	
Participants received lanabecestat 20 mg film-coated oral tablets once daily.	
Reporting group title	Lanabecestat 50 mg
Reporting group description:	
Participants received lanabecestat 50 mg film-coated oral tablets once daily.	

Reporting group values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg
Number of subjects	562	590	570
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 Units: years			
arithmetic mean	72.1	72.3	72.6
standard deviation	± 7.1	± 7.0	± 7.0
Gender categorical Units: Subjects			
Female	348	335	340
Male	214	255	230
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	53	45	55
Not Hispanic or Latino	416	442	423
Unknown or Not Reported	93	103	92
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5	7	6
Asian	64	76	69
Native Hawaiian or Other Pacific Islander	0	1	3
Black or African American	4	5	9
White	387	398	389
More than one race	72	70	62

Unknown or Not Reported	30	33	32
Region of Enrollment Units: Subjects			
United States	196	205	199
Japan	38	43	38
United Kingdom	23	22	23
Portugal	8	8	8
Russia	33	36	31
Spain	25	25	28
Canada	32	33	31
South Korea	19	20	20
Netherlands	9	9	12
China	1	0	1
Taiwan	5	10	9
Poland	39	43	40
Denmark	7	8	8
Italy	23	22	21
Mexico	11	9	9
France	30	33	30
Germany	21	22	17
Czech Republic	42	42	45
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.			
Units: Units on a Scale			
arithmetic mean	30.4	30.6	30.6
standard deviation	± 7.9	± 8.3	± 8.5

Reporting group values	Total		
Number of subjects	1722		
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 Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	1023		
Male	699		

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	153		
Not Hispanic or Latino	1281		
Unknown or Not Reported	288		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	18		
Asian	209		
Native Hawaiian or Other Pacific Islander	4		
Black or African American	18		
White	1174		
More than one race	204		
Unknown or Not Reported	95		
Region of Enrollment Units: Subjects			
United States	600		
Japan	119		
United Kingdom	68		
Portugal	24		
Russia	100		
Spain	78		
Canada	96		
South Korea	59		
Netherlands	30		
China	2		
Taiwan	24		
Poland	122		
Denmark	23		
Italy	66		
Mexico	29		
France	93		
Germany	60		
Czech Republic	129		
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.			
Units: Units on a Scale arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo film-coated oral tablets once daily.	
Reporting group title	Lanabecestat 20 mg
Reporting group description:	
Participants received lanabecestat 20 mg film-coated oral tablets once daily.	
Reporting group title	Lanabecestat 50 mg
Reporting group description:	
Participants received lanabecestat 50 mg film-coated oral tablets once daily.	
Reporting group title	Lanabecestat 20 mg
Reporting group description:	
Participants received lanabecestat 20 mg film-coated oral tablets once daily.	
Reporting group title	Lanabecestat 50 mg
Reporting group description:	
Participants received lanabecestat 50 mg film-coated oral tablets once daily.	
Subject analysis set title	Lanabecestat
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received Lanabecestat film-coated tablets orally.	

Primary: Change from Baseline in Alzheimer´s Disease Assessment Scale- Cognitive Subscale (ADAS-Cog13) Score

End point title	Change from Baseline in Alzheimer´s Disease Assessment Scale- Cognitive Subscale (ADAS-Cog13) Score

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-by-visit interaction, AChEI (acetylcholinesterase Inhibitor) use at baseline, pooled site, and covariates for baseline ADAS-Cog13 total score, age at baseline, and baseline ADAS-Cog13 total score-by-visit interaction.

Analysis Population Description (APD): All randomized 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:	
Baseline, Week 78	

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	460	471	464	
Units: Units on a scale				
least squares mean (standard error)	6.42 (± 1.23)	8.93 (± 1.11)	6.20 (± 1.32)	

Statistical analyses

Statistical analysis title	ADAS-Cog13
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	931
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.129
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.752
upper limit	5.776
Variability estimate	Standard error of the mean
Dispersion value	1.64

Statistical analysis title	ADAS-Cog13
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	924
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.903
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.725
upper limit	3.296
Variability estimate	Standard error of the mean
Dispersion value	1.76

Secondary: Change from Baseline in Alzheimer´s Disease Cooperative Study Activities of Daily Living Inventory Instrumental Items Score (ADCS-iADL)

End point title	Change from Baseline in Alzheimer´s Disease Cooperative Study Activities of Daily Living Inventory Instrumental Items Score (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 model with factors for treatment, visit, treatment-by-visit interaction, AChEI use at baseline, pooled site, and covariates for baseline iADL score, age at baseline, and baseline iADL score-by-visit interaction.
APD: All randomized 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:

Baseline, Week 78

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	357	369	347	
Units: Units on a scale				
least squares mean (standard error)	-3.95 (± 1.27)	-6.91 (± 1.29)	-7.13 (± 1.40)	

Statistical analyses

Statistical analysis title	ADCS-iADL
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	726
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.488
upper limit	0.58
Variability estimate	Standard error of the mean
Dispersion value	1.78

Statistical analysis title	ADCS-iADL
Comparison groups	Placebo v Lanabecestat 50 mg

Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.876
upper limit	0.525
Variability estimate	Standard error of the mean
Dispersion value	1.86

Secondary: Change from Baseline in Functional Activities Questionnaire (FAQ) Score

End point title	Change from Baseline in Functional Activities Questionnaire (FAQ) Score

End point description:

FAQ is a 10-item, caregiver-based questionnaire and was administered to the study partner who was 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 [the activity] but could do now =0; normal =0; has difficulty but does by self =1; requires assistance= 2; Dependent = 3). The maximum FAQ total score is 30, with higher scores indicating greater impairment. LS Mean determined by MMRM model. APD: All randomized 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:

Baseline, Week 78

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	358	369	347	
Units: Units on a scale				
least squares mean (standard error)	3.93 (± 0.81)	5.16 (± 0.85)	3.41 (± 0.91)	

Statistical analyses

Statistical analysis title	FAQ Score
Comparison groups	Placebo v Lanabecestat 20 mg

Number of subjects included in analysis	727
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.285
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.045
upper limit	3.499
Variability estimate	Standard error of the mean
Dispersion value	1.14

Statistical analysis title	FAQ Score
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.661
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.889
upper limit	1.843
Variability estimate	Standard error of the mean
Dispersion value	1.19

Secondary: Change from Baseline on the Integrated Alzheimer's Disease Rating Scale (iADRS) Score

End point title	Change from Baseline 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 higher scores indicating greater impairment. LS Mean was determined by MMRM with factors for treatment, visit, treatment-by-visit interaction, AChEI use at baseline, pooled site, and covariates for baseline iADRS13 total score, age at baseline, and baseline iADRS13 total score-by-visit interaction.
APD: All randomized 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: Baseline, Week 78

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	342	348	333	
Units: Units on a scale				
least squares mean (standard error)	-10.46 (± 1.97)	-15.22 (± 1.90)	-12.43 (± 2.08)	

Statistical analyses

Statistical analysis title	iADRS
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	690
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-4.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.103
upper limit	0.56
Variability estimate	Standard error of the mean
Dispersion value	2.69

Statistical analysis title	iADRS
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	675
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.486
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.573
upper limit	3.62

Variability estimate	Standard error of the mean
Dispersion value	2.82

Secondary: Change from Baseline in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) Score

End point title	Change from Baseline in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) Score

End point description:

The CDR-SB is a rater administered scale and impairment is scored in each of categories: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Impairment is scored on a scale in which no dementia = 0, questionable dementia = 0.5, mild dementia = 1, moderate dementia = 2 and severe dementia = 3. The 6 individual category ratings, or "box scores", were added together to give the CDR-Sum of Boxes which ranges from 0-18, with higher scores indicating greater impairment. LS Mean was determined by MMRM methodology with factors for treatment, visit, treatment-by-visit interaction, AChEI use at baseline, pooled site, and covariates for baseline CDR-SB score, age at baseline, and baseline CDR-SB score-by-visit interaction.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for CDR-SB.

End point type	Secondary

End point timeframe:

Baseline, Week 78

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	369	370	363	
Units: Units on a scale				
least squares mean (standard error)	2.32 (± 0.42)	2.57 (± 0.41)	2.10 (± 0.45)	

Statistical analyses

Statistical analysis title	CDR-SB
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	739
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.663
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	1.391
Variability estimate	Standard error of the mean
Dispersion value	0.57

Statistical analysis title	CDR-SB
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.717
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.423
upper limit	0.983
Variability estimate	Standard error of the mean
Dispersion value	0.6

Secondary: Time to Progression as Measured by Loss of Clinical Dementia Rating (CDR) Global Score Stage

End point title	Time to Progression as Measured by Loss of Clinical Dementia Rating (CDR) Global Score Stage

End point description:

The CDR global score is a composite score calculated using the Washington University CDR-assignment algorithm applied to the 6 individual domain box scores (Morris 1993). The memory domain is considered the primary category that drives the CDR global outcome, and all other domains are secondary. The CDR global score ranges from 0 to 3 (0 = no dementia, 0.5 = questionable dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia).
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for CDR global score.

End point type	Secondary

End point timeframe:

From Loss of 1 Global Stage through Week 78

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	479	500	466	
Units: Days				
median (confidence interval 95%)	379 (367 to 546)	367 (365 to 456)	449 (365 to 491)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Neuropsychiatric Inventory (NPI) Score

End point title	Change from Baseline in Neuropsychiatric Inventory (NPI) Score

End point description:

The NPI is a questionnaire administered to caregivers that quantifies behavioral changes. Each of the 12 behavioral domains the caregiver reports as present are scored for Frequency, scale: 1 (Occasionally) to 4 (Very Frequently), and Severity, scale: 1 (Mild) to 3 (Severe). If the domain is reported by the caregiver as 'Not Affected,' that domain is scored as 0. The individual domain scores are calculated by multiplying the frequency times the severity for each domain. NPI Total Score is calculated by adding the individual domain scores together for all 12 domains, with a scores range from 0 to 144, with higher scores indicating a greater severity of neuropsychiatric disturbance. LS Mean was determined by MMRM methodology.
All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for NPI.

End point type	Secondary

End point timeframe:

Baseline, Week 78

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	351	363	342	
Units: Units on a scale				
least squares mean (standard error)	3.45 (± 1.70)	3.75 (± 1.84)	0.44 (± 1.45)	

Statistical analyses

Statistical analysis title	NPI
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	714
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.899
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.297
upper limit	4.889
Variability estimate	Standard error of the mean
Dispersion value	2.34

Statistical analysis title	NPI
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	693
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.164
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-3.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.267
upper limit	1.238
Variability estimate	Standard error of the mean
Dispersion value	2.16

Secondary: Change from Baseline on the Mini-Mental State Examination (MMSE)

End point title	Change from Baseline on the Mini-Mental State Examination (MMSE)

End point description:

The MMSE is an instrument used to assess a participant's global 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-by-visit interaction, AChEI use at baseline, pooled site, and covariates for baseline MMSE total score, age at baseline, and baseline MMSE total score-by-visit interaction.
APD: All randomized 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:

Baseline, Week 78

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	476	495	477	
Units: Units on a scale				
least squares mean (standard error)	-4.16 (± 0.59)	-5.43 (± 0.58)	-4.31 (± 0.64)	

Statistical analyses

Statistical analysis title	MMSE
Comparison groups	Placebo v Lanabecestat 20 mg

Number of subjects included in analysis	971
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.126
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.891
upper limit	0.362
Variability estimate	Standard error of the mean
Dispersion value	0.82

Statistical analysis title	MMSE
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	953
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.862
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.867
upper limit	1.566
Variability estimate	Standard error of the mean
Dispersion value	0.86

Secondary: Percent Change from Baseline in Concentration of Cerebrospinal fluid (CSF) Biomarker Aβ1-42

End point title	Percent Change from Baseline in Concentration of Cerebrospinal fluid (CSF) Biomarker Aβ1-42

End point description:

Concentration of the peptide Aβ 1-42 in plasma measured by validated immunoassay. LS Mean was determined by Analysis of covariance (ANCOVA) with LOCF (last observation carried forward), terms for treatment, baseline biomarker and age at baseline.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for Aβ1-42.

End point type	Secondary

End point timeframe:

Baseline, Week 71

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	5	
Units: Percentage change in Aβ1-42				
least squares mean (standard error)	23.68 (± 26.76)	-13.87 (± 24.30)	-17.04 (± 23.26)	

Statistical analyses

Statistical analysis title	Aβ1-42
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	9
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.343
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-37.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-122.35
upper limit	47.26
Variability estimate	Standard error of the mean
Dispersion value	37.49

Statistical analysis title	Aβ1-42
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	9
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.276
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-40.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-120.17
upper limit	38.73
Variability estimate	Standard error of the mean
Dispersion value	35.12

Secondary: Percent Change from Baseline in Concentration of CSF Biomarker Aβ1-40

End point title	Percent Change from Baseline in Concentration of CSF Biomarker Aβ1-40

End point description:

Concentration of the peptide Aβ 1-40 in plasma measured by immunoassay. LS Mean was determined by ANCOVA with LOCF (last observation carried forward), terms for treatment, baseline biomarker and age at baseline.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for Aβ1-40.

End point type	Secondary

End point timeframe:

Baseline, Week 71

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	5	
Units: Percentage change in Aβ1-40				
least squares mean (standard error)	24.52 (± 23.08)	-37.42 (± 20.76)	-9.63 (± 20.74)	

Statistical analyses

Statistical analysis title	Aβ1-40
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	9
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.079
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-61.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-132.75
upper limit	8.87
Variability estimate	Standard error of the mean
Dispersion value	31.3

Statistical analysis title	Aβ1-40

Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	9
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.303
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-34.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-104.88
upper limit	36.59
Variability estimate	Standard error of the mean
Dispersion value	31.27

Secondary: Change from Baseline in CSF Biomarker Total Tau

End point title	Change from Baseline in CSF Biomarker Total Tau

End point description:

Cerebrospinal fluid samples were collected for analysis of concentration total tau. LS Mean was determined by ANCOVA with LOCF and with factors for treatment, baseline biomarker and age at baseline.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for CSF Total Tau.

End point type	Secondary

End point timeframe:

Baseline, Week 71

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	5	
Units: Picogram per milliliter (pg/mL)				
least squares mean (standard error)	1.84 (± 9.75)	18.16 (± 9.77)	-11.21 (± 9.32)	

Statistical analyses

Statistical analysis title	CSF Total Tau
Comparison groups	Placebo v Lanabecestat 20 mg

Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.283
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	16.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.015
upper limit	48.659
Variability estimate	Standard error of the mean
Dispersion value	14.29

Statistical analysis title	CSF Total Tau
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.349
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-13.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.929
upper limit	16.82
Variability estimate	Standard error of the mean
Dispersion value	13.21

Secondary: Change from Baseline in CSF Biomarker Phosphorylated Tau

End point title	Change from Baseline in CSF Biomarker Phosphorylated Tau

End point description:

Cerebrospinal fluid samples are collected for analysis of concentration of phosphorylated tau. LS Mean was determined by ANCOVA with LOCF and with factors for treatment, baseline biomarker and age at baseline.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for CSF Phosphorylated Tau.

End point type	Secondary

End point timeframe:

Baseline, Week 71

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	5	
Units: Picogram per milliliter (pg/mL)				
least squares mean (standard error)	2.22 (± 1.54)	3.81 (± 1.49)	0.08 (± 1.41)	

Statistical analyses

Statistical analysis title	CSF Phosphorylated Tau
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.494
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.457
upper limit	6.64
Variability estimate	Standard error of the mean
Dispersion value	2.23

Statistical analysis title	CSF Phosphorylated Tau
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.323
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.743
upper limit	2.481
Variability estimate	Standard error of the mean
Dispersion value	2.04

Secondary: Change From Baseline in Brain Amyloid Burden Using Florbetapir

Amyloid Positron Emission Tomography (PET) Scan

End point title	Change From Baseline in Brain Amyloid Burden Using Florbetapir Amyloid Positron Emission Tomography (PET) Scan

End point description:

Amyloid deposition in the brain is one of the defining neuropathologic findings of Alzheimer's disease. Florbetapir exhibits high affinity specific binding to amyloid plaques. The change from baseline was measured as average standard uptake value ratio (SUVr) in prespecified regions of interest (ROI) assessed by florbetapir amyloid PET imaging in a subset of participants. Centiloid values were generated using SUVr-CER; Navitsky et al. 2018. LS Mean was determined by using ANCOVA methodology with terms for treatment, baseline biomarker and age at baseline.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for brain amyloid burden.

End point type	Secondary

End point timeframe:

Baseline, Week 78

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	10	7	
Units: Centiloids				
least squares mean (standard error)	-2.43 (± 10.47)	-0.21 (± 7.79)	-17.63 (± 9.69)	

Statistical analyses

Statistical analysis title	Florbetapir Amyloid Scan
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.873
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.569
upper limit	31.017
Variability estimate	Standard error of the mean
Dispersion value	13.76

Statistical analysis title	Florbetapir Amyloid Scan
Comparison groups	Placebo v Lanabecestat 50 mg

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.337
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-15.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.488
upper limit	17.096
Variability estimate	Standard error of the mean
Dispersion value	15.43

Secondary: Change from Baseline in Regional Cerebral Blood Flow (rCBF) using Florbetapir Perfusion Scan

End point title	Change from Baseline in Regional Cerebral Blood Flow (rCBF) using Florbetapir Perfusion Scan

End point description:

Florbetapir perfusion evaluated the regional cerebral blood flow (rCBF) as a biomarker of brain function and was performed at the same time as the amyloid florbetapir PET. Cerebral perfusion, especially in temporal and parietal areas, is reduced in AD and this pattern of hypoperfusion closely mirrors the hypometabolism pattern observed using FDG PET. Annualized change is derived as change at LOCF divided by (LOCF date - baseline date) multiplied by 365. LS Mean was determined by ANCOVA with LOCF (last observation carried forward) and with factors for treatment, baseline biomarker and age at baseline.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for rCBF.

End point type	Secondary

End point timeframe:

Baseline, Week 78

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	65	66	
Units: Standard Uptake Value ratio (SUVr)				
least squares mean (standard error)	-0.03 (± 0.01)	-0.03 (± 0.01)	-0.03 (± 0.01)	

Statistical analyses

Statistical analysis title	rCBF
Comparison groups	Placebo v Lanabecestat 20 mg

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.927
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.017
Variability estimate	Standard error of the mean
Dispersion value	0.01

Statistical analysis title	rCBF
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.017
Variability estimate	Standard error of the mean
Dispersion value	0.01

Secondary: Change from Baseline in Whole Brain Volume

End point title	Change from Baseline in Whole Brain Volume

End point description:

Magnetic resonance imaging (MRI) was used to evaluate the effect of lanabecestat on brain atrophy/whole brain volumes. Annualized change is derived as change at LOCF divided by (LOCF date - baseline date) multiplied by 365. LS Mean was determined by ANCOVA with LOCF and with factors for treatment, baseline volumetric magnetic resonance imaging (vMRI), intracranial volume and age at baseline.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for Whole Brain Volume.

End point type	Secondary

End point timeframe:

Baseline, Week 78

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	215	215	214	
Units: cm^3 (cubic centimeter)				
least squares mean (standard error)	-15.76 (± 0.75)	-17.38 (± 0.75)	-18.84 (± 0.76)	

Statistical analyses

Statistical analysis title	Whole Brain Volume
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.708
upper limit	0.464
Variability estimate	Standard error of the mean
Dispersion value	1.06

Statistical analysis title	Whole Brain Volume
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-3.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.172
upper limit	-0.991
Variability estimate	Standard error of the mean
Dispersion value	1.06

Secondary: Population Pharmacokinetics (PK): Apparent Oral Clearance of Lanabecestat

End point title	Population Pharmacokinetics (PK): Apparent Oral Clearance of Lanabecestat

End point description:

The apparent oral clearance of lanabecestat was estimated using a population approach. No covariate effects were assessed as part of this analysis.
APD: All randomized participants who received at least 1 dose of study drug with evaluable PK data.

End point type	Secondary

End point timeframe:

Predose, Week 4, 7, 19, 39, 45 and Week 71 post dose

End point values	Lanabecestat			
Subject group type	Subject analysis set			
Number of subjects analysed	1077			
Units: Liter per hour (L/h)				
geometric mean (geometric coefficient of variation)	17.4 (± 38.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK: Central Volume of Distribution of Lanabecestat

End point title	Population PK: Central Volume of Distribution of Lanabecestat

End point description:

The central volume of distribution for lanabecestat was estimated using a population approach. No covariate effects were assessed as part of this analysis.
APD: All randomized participants who received at least 1 dose of study drug with evaluable PK data.

End point type	Secondary

End point timeframe:

Predose, Week 4, 7, 19, 39, 45 and week 71 post dose

End point values	Lanabecestat			
Subject group type	Subject analysis set			
Number of subjects analysed	1077			
Units: Liters (L)				
geometric mean (geometric coefficient of variation)	77.8 (± 198)			

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 randomized 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	Lanabecestat 20 mg-Period 1
Reporting group description:	
Participants received lanabecestat 20 mg film-coated oral tablets once daily.	
Reporting group title	Lanabecestat 50 mg-Period 1
Reporting group description:	
Participants received lanabecestat 50 mg film-coated oral tablets once daily.	
Reporting group title	Placebo-Period 1
Reporting group description:	
Participants received placebo film-coated oral tablets once daily.	
Reporting group title	Lanabecestat 20 mg-Period 2
Reporting group description:	
Participants from placebo group were randomized to receive lanabecestat 20 mg film-coated oral tablets once daily.	
Reporting group title	Lanabecestat 50 mg-Period 2
Reporting group description:	
Participants from placebo group were randomized to receive lanabecestat 50 mg film-coated oral tablets once daily.	

Serious adverse events	Lanabecestat 20 mg-Period 1	Lanabecestat 50 mg-Period 1	Placebo-Period 1
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 588 (8.50%)	46 / 568 (8.10%)	50 / 558 (8.96%)
number of deaths (all causes)	2	3	5
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
adenocarcinoma of colon			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
adenocarcinoma pancreas			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
bladder transitional cell carcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
brain neoplasm			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
breast cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
colon cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	1 / 568 (0.18%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
colorectal cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
invasive ductal breast carcinoma			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lung adenocarcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
ovarian cancer recurrent			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[1]	0 / 333 (0.00%)	1 / 339 (0.29%)	0 / 347 (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
ovarian cancer stage ii			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[2]	0 / 333 (0.00%)	0 / 339 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pancreatic carcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
papillary thyroid cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
prostate cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[3]	1 / 255 (0.39%)	0 / 229 (0.00%)	1 / 211 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

renal oncocytoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
squamous cell carcinoma of the tongue			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypertension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
peripheral ischaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
thrombosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
death			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
feeling abnormal			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
non-cardiac chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
sudden cardiac death			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Immune system disorders			
anaphylactic reaction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
chronic obstructive pulmonary disease			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
hiccups			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoxia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
lung disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
pleural effusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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 aspiration			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
pneumothorax			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
pulmonary embolism			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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 arrest			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
abnormal behaviour			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
acute psychosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
adjustment disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
aggression			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
confusional state			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
delirium			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	2 / 568 (0.35%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
delusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
mental status changes			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
paranoia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
psychotic disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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

Investigations			
prostatic specific antigen increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[4]	1 / 255 (0.39%)	0 / 229 (0.00%)	0 / 211 (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
Injury, poisoning and procedural complications			
animal bite			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
ankle fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
brain contusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
clavicle fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
craniocerebral injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
fall			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 588 (0.51%)	5 / 568 (0.88%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 5	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 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
femur fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	1 / 568 (0.18%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fibula fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
forearm fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
heat exhaustion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hip fracture			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
humerus fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lumbar vertebral fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	1 / 568 (0.18%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pelvic fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
post procedural complication			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pubis fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	2 / 568 (0.35%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
rib fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	2 / 568 (0.35%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

road traffic accident			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
spinal compression fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
spinal fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
subdural haematoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tibia fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
upper limb fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
wrist fracture			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
Congenital, familial and genetic disorders			
gastrointestinal arteriovenous malformation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
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 coronary syndrome			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	1 / 568 (0.18%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
acute myocardial infarction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
atrial fibrillation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	2 / 568 (0.35%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrial flutter			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrioventricular block complete			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
cardiac arrest			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
cardiac failure congestive			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
cardio-respiratory arrest			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
chronotropic incompetence			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
coronary artery disease			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
myocardial infarction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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

sinus node dysfunction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 588 (0.34%)	0 / 568 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
stress cardiomyopathy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
trifascicular block			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
ventricular fibrillation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
brain injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cerebellar haematoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
cerebral infarction			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
cerebrovascular accident			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	2 / 568 (0.35%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cognitive disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
coma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dementia alzheimer's type			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
device malfunction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
dizziness			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

encephalopathy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
generalised tonic-clonic seizure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemorrhage intracranial			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
headache			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
presyncope			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
seizure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	3 / 588 (0.51%)	3 / 568 (0.53%)	3 / 558 (0.54%)
occurrences causally related to treatment / all	2 / 3	2 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
toxic encephalopathy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
transient ischaemic attack			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
iron deficiency anaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
vertigo positional			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
colitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
colitis ischaemic			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
constipation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	2 / 568 (0.35%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diverticulum			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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 haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
inguinal hernia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
intestinal obstruction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
peptic ulcer perforation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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

rectal prolapse			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
vomiting			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
Hepatobiliary disorders			
cholecystitis acute			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
cholelithiasis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
stress urinary incontinence			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

cervical spinal stenosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
muscle haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
muscle spasms			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
myalgia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	0 / 558 (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
osteoarthritis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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			
bacteraemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bronchitis viral			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
cellulitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
cellulitis orbital			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
epididymitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[5]	1 / 255 (0.39%)	0 / 229 (0.00%)	1 / 211 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
erysipelas			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
liver abscess			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	1 / 568 (0.18%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
orchitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[6]	0 / 255 (0.00%)	0 / 229 (0.00%)	1 / 211 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

pneumonia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	1 / 568 (0.18%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
sepsis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
sinusitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
urinary tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urosepsis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	1 / 568 (0.18%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
dehydration			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	2 / 588 (0.34%)	1 / 568 (0.18%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoglycaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (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
hyponatraemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	2 / 568 (0.35%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Lanabecestat 20 mg-Period 2	Lanabecestat 50 mg-Period 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	1 / 12 (8.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
adenocarcinoma of colon			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
adenocarcinoma pancreas			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bladder transitional cell carcinoma			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
brain neoplasm			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colon cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colorectal cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
invasive ductal breast carcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung adenocarcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

ovarian cancer recurrent			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[1]	0 / 9 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ovarian cancer stage ii			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[2]	0 / 9 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancreatic carcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
papillary thyroid cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
prostate cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[3]	0 / 5 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal oncocytoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
squamous cell carcinoma of the tongue			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral ischaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
death			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
feeling abnormal			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
non-cardiac chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sudden cardiac death			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
anaphylactic reaction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hiccups			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoxia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia aspiration			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

respiratory arrest			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
abnormal behaviour			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute psychosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
adjustment disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
aggression			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
confusional state			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
delirium			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
delusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mental status changes			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
paranoia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
psychotic disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
prostatic specific antigen increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[4]	0 / 5 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
animal bite			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ankle fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
brain contusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
clavicle fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
craniocerebral injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fall			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
femoral neck fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

femur fracture				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
fibula fracture				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
forearm fracture				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
heat exhaustion				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
hip fracture				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
humerus fracture				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
lumbar vertebral fracture				
alternative dictionary used: MedDRA 21.1				

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pelvic fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
post procedural complication			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pubis fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rib fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
road traffic accident			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal compression fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

spinal fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
subdural haematoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tibia fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper limb fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
wrist fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
gastrointestinal arteriovenous malformation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

acute coronary syndrome				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
acute myocardial infarction				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
atrial fibrillation				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
atrial flutter				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
atrioventricular block complete				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
cardiac arrest				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
cardiac failure congestive				
alternative dictionary used: MedDRA 21.1				

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardio-respiratory arrest			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
chronotropic incompetence			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
coronary artery disease			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sinus node dysfunction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
stress cardiomyopathy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

trifascicular block			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ventricular fibrillation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
brain injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebellar haematoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral infarction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebrovascular accident			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cognitive disorder			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
coma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dementia alzheimer's type			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
device malfunction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
encephalopathy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
generalised tonic-clonic seizure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

haemorrhage intracranial				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
headache				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
presyncope				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
seizure				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
syncope				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
toxic encephalopathy				
alternative dictionary used: MedDRA 21.1				
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
transient ischaemic attack				
alternative dictionary used: MedDRA 21.1				

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
iron deficiency anaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
vertigo positional			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
colitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis ischaemic			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
constipation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
diverticulum			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
inguinal hernia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal obstruction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peptic ulcer perforation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal prolapse			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
cholecystitis acute			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholelithiasis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
stress urinary incontinence			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
cervical spinal stenosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
muscle haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
muscle spasms			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myalgia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteoarthritis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
bacteraemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis viral			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cellulitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cellulitis orbital			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
epididymitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[5]	0 / 5 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
erysipelas			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
liver abscess			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
orchitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[6]	0 / 5 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

sinusitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urosepsis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dehydration			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoglycaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyponatraemia			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

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

Non-serious adverse events	Lanabecestat 20 mg-Period 1	Lanabecestat 50 mg-Period 1	Placebo-Period 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 588 (11.73%)	76 / 568 (13.38%)	48 / 558 (8.60%)
Investigations			
blood glucose decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	0 / 568 (0.00%)	0 / 558 (0.00%)
occurrences (all)	0	0	0
thyroxine decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 588 (0.00%)	2 / 568 (0.35%)	0 / 558 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	32 / 588 (5.44%)	34 / 568 (5.99%)	21 / 558 (3.76%)
occurrences (all)	37	49	34

General disorders and administration site conditions			
influenza like illness			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	4 / 568 (0.70%)	1 / 558 (0.18%)
occurrences (all)	1	4	1
Eye disorders			
glaucoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	4 / 588 (0.68%)	3 / 568 (0.53%)	5 / 558 (0.90%)
occurrences (all)	4	3	5
Reproductive system and breast disorders			
benign prostatic hyperplasia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[7]	4 / 255 (1.57%)	3 / 229 (1.31%)	4 / 211 (1.90%)
occurrences (all)	4	3	4
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	29 / 588 (4.93%)	29 / 568 (5.11%)	17 / 558 (3.05%)
occurrences (all)	35	39	19
Psychiatric disorders			
confusional state			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	4 / 588 (0.68%)	9 / 568 (1.58%)	2 / 558 (0.36%)
occurrences (all)	4	9	2
psychotic disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	0 / 568 (0.00%)	0 / 558 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
hyperlipidaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 588 (0.17%)	1 / 568 (0.18%)	1 / 558 (0.18%)
occurrences (all)	1	1	1

Non-serious adverse events	Lanabecestat 20 mg-Period 2	Lanabecestat 50 mg-Period 2	

Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 14 (35.71%)	1 / 12 (8.33%)	
Investigations blood glucose decreased alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all) thyroxine decreased alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1	 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	
Injury, poisoning and procedural complications fall alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	 0 / 14 (0.00%) 0	 0 / 12 (0.00%) 0	
General disorders and administration site conditions influenza like illness alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1	 0 / 12 (0.00%) 0	
Eye disorders glaucoma alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1	 0 / 12 (0.00%) 0	
Reproductive system and breast disorders benign prostatic hyperplasia alternative dictionary used: MedDRA 21.1 subjects affected / exposed[7] occurrences (all)	 1 / 5 (20.00%) 1	 0 / 7 (0.00%) 0	
Gastrointestinal disorders diarrhoea alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
confusional state			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
psychotic disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
hyperlipidaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

Notes:

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

An independent assessment concluded the trial was not likely to meet the primary endpoint upon completion and therefore, trial stopped for futility.

Notes: