Clinical trial results:
A 24-Month, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy, Safety, Tolerability, Biomarker and Pharmacokinetics Study of AZD3293 in Early Alzheimer's Disease (The AMARANTH Study)

Summary

EudraCT number	2014-002601-38
Trial protocol	GB BE DE ES HU FR IT
Global end of trial date	04 October 2018

Results information

Result version number	v2 (current)
This version publication date	15 August 2019
First version publication date	27 June 2019
Version creation reason	• Correction of full data set Correction of full data set

Trial information

Trial identification

Sponsor protocol code	I8D-MC-AZES

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02245737
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16023

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

Global end of trial reached?	Yes
Global end of trial date	04 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the efficacy and safety of lanabecestat compared with placebo administered for 104 weeks in the treatment of early Alzheimer´s disease. The study will test the hypothesis that lanabecestat is a disease-modifying treatment for participants with early Alzheimer´s disease, defined as the continuum of participants with mild cognitive impairment (MCI) due to Alzheimer´s disease and participants diagnosed with mild dementia of the Alzheimer´s type, as measured by change from baseline on the 13-item Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog13) score at week 104 in each of the 2 lanabecestat treatment groups compared with placebo.

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	30 September 2014
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	Romania: 5
Country: Number of subjects enrolled	Puerto Rico: 36
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	United States: 521
Country: Number of subjects enrolled	Japan: 183
Country: Number of subjects enrolled	United Kingdom: 250
Country: Number of subjects enrolled	Spain: 216
Country: Number of subjects enrolled	Canada: 180
Country: Number of subjects enrolled	Korea, Republic of: 70
Country: Number of subjects enrolled	Belgium: 50

Country: Number of subjects enrolled	Poland: 159
Country: Number of subjects enrolled	Italy: 132
Country: Number of subjects enrolled	Australia: 131
Country: Number of subjects enrolled	France: 117
Country: Number of subjects enrolled	Germany: 143
Worldwide total number of subjects	2218
EEA total number of subjects	1097

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)	423
From 65 to 84 years	1770
85 years and over	25

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

No Text Available

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	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	740	739	739
Received at least 1 Dose of Study drug	738	736	735
Completed	187	184	168
Not completed	553	555	571
Adverse event, serious fatal	2	4	4
Condition Worsened	9	10	9
Physician decision	6	3	6
Consent withdrawn by subject	40	41	44
Eligibility Criteria No Longer Met	2	4	4
Adverse event, non-fatal	23	26	33
Withdrawal due to Caregiver Circumstance	10	20	22
Sponsor Decision	445	430	432
Lost to follow-up	2	5	4
Other Selected by Investigator	9	10	10
Initiation of Symptomatic AD medication	2	-	-
Protocol deviation	3	2	3

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	740	739	739
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	71.4	71.2	71.2
standard deviation	± 6.9	± 7.5	± 7.0
Gender categorical Units: Subjects			
Female	398	395	384
Male	342	344	355
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	43	26	24
Not Hispanic or Latino	626	650	644
Unknown or Not Reported	71	63	71
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	85	85	102
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	5	6
White	598	609	593
More than one race	0	0	0

Unknown or Not Reported	52	40	38
Region of Enrollment Units: Subjects			
Puerto Rico	13	11	12
Romania	1	2	2
Hungary	7	12	6
United States	171	171	179
Japan	48	57	78
United Kingdom	85	87	78
Spain	74	77	65
Canada	58	59	63
South Korea	30	24	16
Belgium	20	15	15
Poland	58	51	50
Italy	45	38	49
Australia	38	55	38
France	45	36	36
Germany	47	44	52
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	28.6	29.0	28.5
standard deviation	± 7.9	± 7.7	± 8.2

Reporting group values	Total		
Number of subjects	2218		
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	1177		
Male	1041		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	93		

Not Hispanic or Latino	1920		
Unknown or Not Reported	205		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	272		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	16		
White	1800		
More than one race	0		
Unknown or Not Reported	130		
Region of Enrollment Units: Subjects			
Puerto Rico	36		
Romania	5		
Hungary	25		
United States	521		
Japan	183		
United Kingdom	250		
Spain	216		
Canada	180		
South Korea	70		
Belgium	50		
Poland	159		
Italy	132		
Australia	131		
France	117		
Germany	143		
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.	

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

End point title	Change from Baseline on the 13-item Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog13)

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, disease status at baseline, apolipoprotein E4 (APOE4) status, acetylcholinesterase inhibitor (AChEI) use at baseline, pooled country, and covariates for baseline ADAS-Cog13 total score-by-visit interaction. Analysis Population Description: 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 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	723	722	708	
Units: Units on a scale				
least squares mean (standard error)	10.31 (± 0.55)	9.38 (± 0.56)	10.72 (± 0.58)	

Statistical analyses

Statistical analysis title	ADAS-Cog13
Comparison groups	Placebo v Lanabecestat 20 mg

Number of subjects included in analysis	1445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.232
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.447
upper limit	0.594
Variability estimate	Standard error of the mean
Dispersion value	0.77

Statistical analysis title	ADAS-Cog13
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	1431
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.599
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.124
upper limit	1.947
Variability estimate	Standard error of the mean
Dispersion value	0.78

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

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

End point description:

The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire answered by the participant's caregiver. The ADCS-ADL measures both basic and instrumental activities of daily living by participants. The range for the ADCS-iADL is 0-59 with higher scores reflecting better performance. LS Mean was determined by MMRM model with factors for treatment, visit, treatment-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, pooled country, and covariates for baseline 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 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	702	700	674	
Units: Units on a scale				
least squares mean (standard error)	-8.87 (± 0.60)	-8.84 (± 0.61)	-8.79 (± 0.63)	

Statistical analyses

Statistical analysis title	ADCS-iADL
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	1402
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.971
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.609
upper limit	1.669
Variability estimate	Standard error of the mean
Dispersion value	0.83

Statistical analysis title	ADCS-iADL
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	1376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.923
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	1.743
Variability estimate	Standard error of the mean
Dispersion value	0.85

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

End point title	Change from Baseline on the 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 was calculated by MMRM.
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 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	699	697	674	
Units: Units on a scale				
least squares mean (standard error)	6.09 (± 0.38)	5.96 (± 0.39)	6.71 (± 0.40)	

Statistical analyses

Statistical analysis title	FAQ Score
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	1396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.796
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.172
upper limit	0.899
Variability estimate	Standard error of the mean
Dispersion value	0.53

Statistical analysis title	FAQ Score
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	1373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.252
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.437
upper limit	1.66
Variability estimate	Standard error of the mean
Dispersion value	0.53

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 with higher scores indicating greater impairment. LS Mean was determined by MMRM methodology with factors for treatment, visit, treatment-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, pooled country, 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 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	696	689	662	
Units: Units on a scale				
least squares mean (standard error)	-19.56 (± 0.99)	-18.45 (± 1.02)	-19.69 (± 1.05)	

Statistical analyses

Statistical analysis title	iADRS
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	1385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.428
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.637
upper limit	3.852
Variability estimate	Standard error of the mean
Dispersion value	1.4

Statistical analysis title	iADRS
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	1358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.926
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.918
upper limit	2.655
Variability estimate	Standard error of the mean
Dispersion value	1.42

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

End point title	Change from Baseline on 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 of the following 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, disease status at baseline, APOE4 status, AChEI use at baseline, pooled country, 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 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	704	705	676	
Units: Units on a scale				
least squares mean (standard error)	3.02 (± 0.17)	3.17 (± 0.17)	3.17 (± 0.18)	

Statistical analyses

Statistical analysis title	CDR-SB
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	1409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.533
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.322
upper limit	0.622
Variability estimate	Standard error of the mean
Dispersion value	0.24

Statistical analysis title	CDR-SB
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	1380
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.537
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.328
upper limit	0.63
Variability estimate	Standard error of the mean
Dispersion value	0.24

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:

Baseline through Loss of 1 Global Stage or Week 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	716	714	696	
Units: Days				
median (confidence interval 95%)	548 (547 to 554)	547 (545 to 550)	548 (545 to 553)	

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 indicated a greater severity of neuropsychiatric disturbance. LS Mean was determined by MMRM methodology.
APD: 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 104	

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	697	695	663	
Units: Units on a scale				
least squares mean (standard error)	3.22 (± 0.81)	4.99 (± 0.83)	4.67 (± 0.85)	

Statistical analyses

Statistical analysis title	NPI
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	1392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.116
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.441
upper limit	3.986
Variability estimate	Standard error of the mean
Dispersion value	1.13

Statistical analysis title	NPI
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	1360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.208
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	1.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.808
upper limit	3.704
Variability estimate	Standard error of the mean
Dispersion value	1.15

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 higher score indicating better cognitive performance. LS Mean was determined by MMRM methodology with factors for treatment, visit, treatment-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, pooled country, 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 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	723	725	709	
Units: Units on a scale				
least squares mean (standard error)	-5.50 (± 0.26)	-5.18 (± 0.26)	-5.49 (± 0.27)	

Statistical analyses

Statistical analysis title	MMSE
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	1448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.379
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0.32

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.391
upper limit	1.027
Variability estimate	Standard error of the mean
Dispersion value	0.36

Statistical analysis title	MMSE
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	1432
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.992
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.714
upper limit	0.721
Variability estimate	Standard error of the mean
Dispersion value	0.37

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

End point title	Pharmacodynamics (PD): 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 97

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	66	79	
Units: Percentage change in Aβ1-42				
least squares mean (standard error)	-2.64 (± 2.07)	-53.91 (± 2.04)	-68.13 (± 1.87)	

Statistical analyses

Statistical analysis title	Aβ1-42
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-51.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.963
upper limit	-45.578
Variability estimate	Standard error of the mean
Dispersion value	2.89

Statistical analysis title	Aβ1-42
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-65.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-70.947
upper limit	-60.022
Variability estimate	Standard error of the mean
Dispersion value	2.77

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

End point title	PD: 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 97

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	66	79	
Units: Percentage change in Aβ1-40				
least squares mean (standard error)	-1.92 (± 1.77)	-59.90 (± 1.74)	-75.17 (± 1.60)	

Statistical analyses

Statistical analysis title	Aβ1-40
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-57.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.865
upper limit	-53.108
Variability estimate	Standard error of the mean
Dispersion value	2.47

Statistical analysis title	Aβ1-40
Comparison groups	Placebo v Lanabecestat 50 mg

Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-73.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-77.926
upper limit	-68.575
Variability estimate	Standard error of the mean
Dispersion value	2.37

Secondary: Change from Baseline in CSF Total Tau

End point title	Change from Baseline in CSF Total Tau

End point description:

Cerebrospinal fluid samples are collected for analysis of concentration total tau. LS Mean was determined by ANCOVA with LOCF and with factors for treatment, disease status at baseline, 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 97

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	66	79	
Units: Picogram per milliliter (pg/mL)				
least squares mean (standard error)	12.39 (± 8.05)	-7.48 (± 8.01)	-2.92 (± 7.30)	

Statistical analyses

Statistical analysis title	CSF Total Tau
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-19.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.21
upper limit	2.464
Variability estimate	Standard error of the mean
Dispersion value	11.33

Statistical analysis title	CSF Total Tau
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.157
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-15.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.555
upper limit	5.938
Variability estimate	Standard error of the mean
Dispersion value	10.78

Secondary: Change from Baseline in CSF Phosphorylated Tau

End point title	Change from Baseline in CSF Phosphorylated Tau

End point description:

Cerebrospinal fluid samples are collected for analysis of concentrations of phosphorylated tau. LS Mean was determined by ANCOVA with LOCF and with factors for treatment, disease status at baseline, 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 97

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	66	79	
Units: Picogram per milliliter (pg/mL)				
least squares mean (standard error)	0.47 (± 0.95)	-2.16 (± 0.94)	-1.66 (± 0.85)	

Statistical analyses

Statistical analysis title	CSF Phosphorylated Tau
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.243
upper limit	-0.002
Variability estimate	Standard error of the mean
Dispersion value	1.33

Statistical analysis title	CSF Phosphorylated Tau
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.618
upper limit	0.373
Variability estimate	Standard error of the mean
Dispersion value	1.27

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 ROI assessed by florbetapir amyloid PET imaging in a subset of participants. The Centiloid scale standardizes quantitative brain amyloid PET results to allow cross-tracer and cross-methodology comparisons. The Centiloid scale anchor points are 0 and 100, where 0 represents a high-certainty amyloid negative scan and 100 represents the amount of global amyloid deposition found in a typical AD scans. Florbetapir SUVr was converted to the Centiloid scale using the following conversion: Florbetapir Centiloids = 183 x SUVr - 177 LS Mean was determined by ANCOVA .
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 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	127	116	
Units: Units on a scale				
least squares mean (standard error)	-2.08 (± 1.86)	-15.76 (± 1.89)	-19.74 (± 1.97)	

Statistical analyses

Statistical analysis title	Florbetapir Amyloid Scan
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-13.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.785
upper limit	-8.574
Variability estimate	Standard error of the mean
Dispersion value	2.6

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

Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-17.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.887
upper limit	-12.428
Variability estimate	Standard error of the mean
Dispersion value	2.66

Secondary: Change From Baseline in Tau PET (Flortaucipir F18)

End point title	Change From Baseline in Tau PET (Flortaucipir F18)

End point description:

Tau PET tracer (flortaucipir F18) longitudinal study measured whether lanabecestat, in patients with mild AD dementia, affected tau density and distribution over time. It was planned that up to 4 scans would be performed over 3 years at sites with access to flortaucipir F 18. The outcome reported is the composite summary of SUVRs normalized to the signal intensity in white matter. Annualized change is derived as change at LOCF divided by (LOCF date - baseline date) multiplied by 365. LS Mean was determined by ANCOVA methodology with factors for treatment, disease status at baseline, baseline biomarker and age at baseline. Baseline defined to be within 28 days of starting study drug.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data for Tau PET.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	97	94	93	
Units: Standard Uptake Value ratio (SUVr)				
least squares mean (standard error)	0.04 (± 0.01)	0.03 (± 0.01)	0.03 (± 0.01)	

Statistical analyses

Statistical analysis title	Flortaucipir F18
Comparison groups	Placebo v Lanabecestat 20 mg

Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.426
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.014
Variability estimate	Standard error of the mean
Dispersion value	0.01

Statistical analysis title	Flortaucipir F18
Comparison groups	Placebo v Lanabecestat 50 mg
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.029
upper limit	0.018
Variability estimate	Standard error of the mean
Dispersion value	0.01

Secondary: Change From Baseline in Brain Metabolism Using Fluorodeoxyglucose (FDG)

End point title	Change From Baseline in Brain Metabolism Using Fluorodeoxyglucose (FDG)

End point description:

Fluorodeoxyglucose (FDG) PET evaluates the regional brain metabolic rates for glucose as a sensitive, in vivo metabolic index of brain function. The outcome reported is the composite summary of the standard uptake value ratio (SUVR) normalized to the pons + vermis assessed with composite meta and composite meta automated anatomical labeling atlas (ALL). Annualized change is derived as change at LOCF divided by (LOCF date - baseline date) multiplied by 365. LS Mean was determined by ANCOVA methodology with factors for treatment, disease status at baseline, baseline biomarker and age at baseline. Baseline defined to be within 28 days of starting study drug.
APD: All randomized participants who received at least one dose of study drug and have baseline and at least one post-baseline data of brain metabolism.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	95	82	
Units: Standard Uptake Value ratio (SUVr)				
least squares mean (standard error)	-0.04 (± 0.00)	-0.05 (± 0.00)	-0.05 (± 0.00)	

Statistical analyses

Statistical analysis title	FDG
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.003
Variability estimate	Standard error of the mean
Dispersion value	0

Statistical analysis title	FDG
Comparison groups	Lanabecestat 50 mg v Placebo
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.568
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.007
Variability estimate	Standard error of the mean
Dispersion value	0

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 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 methodology with factors for treatment, baseline vMRI, intracranial volume, disease status at baseline 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 104

End point values	Placebo	Lanabecestat 20 mg	Lanabecestat 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	565	582	550	
Units: cm^3 (cubic centimeter)				
least squares mean (standard error)	-14.16 (± 0.34)	-16.49 (± 0.33)	-17.34 (± 0.34)	

Statistical analyses

Statistical analysis title	Whole Brain Volume
Comparison groups	Placebo v Lanabecestat 20 mg
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.258
upper limit	-1.413
Variability estimate	Standard error of the mean
Dispersion value	0.47

Statistical analysis title	Whole Brain Volume
Comparison groups	Placebo v Lanabecestat 50 mg

Number of subjects included in analysis	1115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference (Final Values)
Point estimate	-3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.118
upper limit	-2.247
Variability estimate	Standard error of the mean
Dispersion value	0.48

Secondary: Pharmacokinetics (PK): Plasma Concentration of Lanabecestat

End point title	Pharmacokinetics (PK): Plasma Concentration of

End point description:

Plasma Concentration of Lanabecestat.
APD: All randomized participants who received at least one dose of study drug and have evaluable PK data.

End point type	Secondary

End point timeframe:

Week 4, post dose prior to departure from the clinic

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No arm comparison analyses were planned or conducted.

End point values	Lanabecestat 20 mg	Lanabecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	697	662		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)	67.7 (± 49.1)	213 (± 149)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up To 104 weeks

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug. There are gender specific adverse events, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

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	Placebo

Reporting group description:

Participants received placebo film-coated oral tablets once daily.

Serious adverse events	Lanabecestat 20 mg	Lanabecestat 50 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	117 / 736 (15.90%)	147 / 735 (20.00%)	108 / 738 (14.63%)
number of deaths (all causes)	4	4	2
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
acoustic neuroma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
acute myeloid leukaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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

adenocarcinoma of colon			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
basal cell carcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bile duct adenocarcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bladder neoplasm			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
breast cancer male			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[1]	1 / 344 (0.29%)	0 / 354 (0.00%)	0 / 341 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
breast cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
breast cancer recurrent			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
colon cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	2 / 735 (0.27%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
endometrial adenocarcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[2]	0 / 392 (0.00%)	0 / 381 (0.00%)	1 / 397 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemangioma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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	2 / 736 (0.27%)	2 / 735 (0.27%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
laryngeal squamous cell carcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
lentigo maligna			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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 adenocarcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	3 / 735 (0.41%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lung neoplasm			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lymphoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
lung neoplasm malignant			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	0 / 735 (0.00%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
malignant melanoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
malignant melanoma in situ			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
malignant neoplasm of unknown primary site			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
metastases to bone			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
metastases to lymph nodes			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neuroendocrine tumour			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ovarian adenoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[3]	0 / 392 (0.00%)	1 / 381 (0.26%)	0 / 397 (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
pancreatic carcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
prostate cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[4]	2 / 344 (0.58%)	2 / 354 (0.56%)	2 / 341 (0.59%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

prostatic adenoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[5]	0 / 344 (0.00%)	0 / 354 (0.00%)	1 / 341 (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
rectal adenoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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 adenocarcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
rectal cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
small cell lung cancer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
squamous cell carcinoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
transitional cell carcinoma			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
aortic aneurysm			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
deep vein thrombosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	0 / 735 (0.00%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
granulomatosis with polyangiitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haematoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
hypertension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
hypertensive crisis			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypotension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
orthostatic hypotension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
peripheral artery stenosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
temporal arteritis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	0 / 735 (0.00%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
thrombophlebitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
venous thrombosis limb			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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

Surgical and medical procedures			
cardiac pacemaker insertion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
cataract operation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
hip arthroplasty			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
inguinal hernia repair			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
spinal operation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
synovial cyst removal			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tumour excision			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urethral repair			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
vocal cord operation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	4 / 736 (0.54%)	4 / 735 (0.54%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 4	0 / 4	1 / 1
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	2 / 736 (0.27%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyrexia			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sudden death			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
systemic inflammatory response syndrome			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
drug hypersensitivity			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
seasonal allergy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
Reproductive system and breast disorders			
benign prostatic hyperplasia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[6]	1 / 344 (0.29%)	1 / 354 (0.28%)	2 / 341 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
postmenopausal haemorrhage			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed[7]	1 / 392 (0.26%)	0 / 381 (0.00%)	0 / 397 (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
Respiratory, thoracic and mediastinal disorders			
acute respiratory distress syndrome			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
asthma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cystic lung disease			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
dyspnoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
obstructive airways disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
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 aspiration			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
pneumothorax			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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	1 / 736 (0.14%)	2 / 735 (0.27%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pulmonary oedema			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
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 arrest			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
sleep apnoea syndrome			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
stridor			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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

Psychiatric disorders			
abnormal behaviour			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
acute psychosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	0 / 735 (0.00%)	0 / 738 (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
aggression			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	2 / 735 (0.27%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
agitation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	2 / 735 (0.27%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
anxiety			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	2 / 735 (0.27%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
confusional state			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
delirium			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	2 / 736 (0.27%)	5 / 735 (0.68%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
depression			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	4 / 735 (0.54%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
depressive symptom			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	3 / 735 (0.41%)	0 / 738 (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
device failure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
hallucination			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
hallucination, auditory			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
hallucination, olfactory			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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

paranoia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
psychotic disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
schizophrenia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
suicidal ideation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	0 / 738 (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
suicide attempt			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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			
blood potassium decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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			
accidental overdose			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
accidental poisoning			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
alcohol poisoning			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
ankle fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cervical vertebral fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
chemical burn of gastrointestinal tract			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
clavicle fracture			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
contusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	0 / 738 (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
fall			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	8 / 736 (1.09%)	4 / 735 (0.54%)	6 / 738 (0.81%)
occurrences causally related to treatment / all	0 / 8	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
femur fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
femoral neck fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	2 / 735 (0.27%)	0 / 738 (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
fibula fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
forearm fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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

head injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hip fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 736 (0.41%)	2 / 735 (0.27%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	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	0 / 736 (0.00%)	2 / 735 (0.27%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
jaw fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
lacrimal structure injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
ligament rupture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
lumbar vertebral fracture			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
multiple injuries			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
overdose			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pelvic fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
periprosthetic fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
post procedural haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
pubis fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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

radius fracture alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	2 / 735 (0.27%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	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 / 736 (0.00%)	0 / 735 (0.00%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
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 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
skin laceration alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
skull fracture alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
spinal compression fracture alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	3 / 738 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
spinal fracture alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
subdural haematoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	3 / 735 (0.41%)	3 / 738 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
subdural haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
thoracic vertebral fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
tibia fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ulna fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
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 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

wrist fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
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	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
Cardiac disorders			
acute coronary syndrome			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	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 / 736 (0.00%)	2 / 735 (0.27%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
angina pectoris			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
angina unstable			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
atrial fibrillation			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	1 / 735 (0.14%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrial flutter			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bifascicular block			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
bradycardia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
cardiac failure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	2 / 735 (0.27%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	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 / 736 (0.14%)	0 / 735 (0.00%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
cardiac tamponade			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
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 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
coronary artery thrombosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
myocardial infarction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	0 / 735 (0.00%)	4 / 738 (0.54%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sinus node dysfunction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sinus bradycardia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
stress cardiomyopathy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

supraventricular extrasystoles			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
supraventricular tachycardia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tachycardia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
tricuspid valve incompetence			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
Nervous system disorders			
altered state of consciousness			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
central nervous system lesion			
alternative dictionary used:			

MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cerebral haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	2 / 735 (0.27%)	3 / 738 (0.41%)
occurrences causally related to treatment / all	0 / 0	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
cerebral haematoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
cerebral microhaemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	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	3 / 736 (0.41%)	1 / 735 (0.14%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cervical radiculopathy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cholinergic syndrome			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
cognitive disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
dementia with lewy bodies			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
dizziness			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dyskinesia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
epilepsy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
generalised tonic-clonic seizure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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

headache			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypertensive encephalopathy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoaesthesia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
intraventricular haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
partial seizures			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
petit mal epilepsy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
presyncope			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sciatica			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
seizure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	2 / 735 (0.27%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
subarachnoid haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	6 / 736 (0.82%)	7 / 735 (0.95%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	3 / 6	2 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
thalamic infarction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
transient ischaemic attack			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	2 / 735 (0.27%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ulnar nerve palsy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vasogenic cerebral oedema			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vocal cord paresis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
vestibular disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
Eye disorders			
cataract			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pterygium			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
retinal detachment			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
retinal haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal discomfort			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
alcoholic pancreatitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
anal incontinence			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
coeliac artery stenosis			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
colitis microscopic			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
colitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
constipation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diarrhoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
enlarged uvula			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
faecaloma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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

femoral hernia incarcerated			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
food poisoning			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastric ulcer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
gastritis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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	1 / 736 (0.14%)	1 / 735 (0.14%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
haemorrhoids			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	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	2 / 736 (0.27%)	3 / 735 (0.41%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intestinal mass			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
intestinal obstruction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	3 / 735 (0.41%)	0 / 738 (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
large intestine polyp			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	2 / 735 (0.27%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
pancreatitis acute			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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

rectal prolapse			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	0 / 735 (0.00%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
small intestinal obstruction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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	1 / 736 (0.14%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
cholelithiasis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
drug-induced liver injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
angioedema			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
drug eruption			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
psoriasis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
calculus bladder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary retention			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	1 / 735 (0.14%)	0 / 738 (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
urge incontinence			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
arthritis			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 736 (0.14%)	2 / 735 (0.27%)	0 / 738 (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
back pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
bone lesion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
foot deformity			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
infrapatellar fat pad inflammation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
intervertebral disc compression			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
intervertebral disc protrusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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

lumbar spinal stenosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
mobility decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
musculoskeletal pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
musculoskeletal chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
myofascial pain syndrome			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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	2 / 736 (0.27%)	1 / 735 (0.14%)	4 / 738 (0.54%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
osteolysis			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
osteoporotic fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
pain in extremity			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
spinal column stenosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vertebral foraminal stenosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
bone abscess			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
bronchitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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 / 736 (0.14%)	2 / 735 (0.27%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
clostridium difficile colitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
diverticulitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	3 / 735 (0.41%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
endocarditis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatic cyst infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

human anaplasmosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
influenza			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 736 (0.27%)	4 / 735 (0.54%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intervertebral discitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower respiratory tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower respiratory tract infection viral			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
ophthalmic herpes zoster			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
peritonsillitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
pneumonia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 736 (0.41%)	3 / 735 (0.41%)	6 / 738 (0.81%)
occurrences causally related to treatment / all	0 / 3	0 / 3	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
sepsis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
septic arthritis streptococcal			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
septic shock			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
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 / 736 (0.14%)	3 / 735 (0.41%)	6 / 738 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

urinary tract infection pseudomonal			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
vestibular neuronitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
dehydration			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	4 / 736 (0.54%)	5 / 735 (0.68%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
electrolyte imbalance			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypercalcaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	1 / 738 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hyperglycaemia			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 736 (0.00%)	1 / 735 (0.14%)	0 / 738 (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
hypoglycaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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	2 / 736 (0.27%)	1 / 735 (0.14%)	0 / 738 (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
hypokalaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
hypophosphataemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 736 (0.14%)	0 / 735 (0.00%)	0 / 738 (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
lactic acidosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 736 (0.00%)	0 / 735 (0.00%)	2 / 738 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	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.

[7] - 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	Lanabecestat 50 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	357 / 736 (48.51%)	361 / 735 (49.12%)	340 / 738 (46.07%)
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	71 / 736 (9.65%)	73 / 735 (9.93%)	69 / 738 (9.35%)
occurrences (all)	95	111	86
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	43 / 736 (5.84%)	51 / 735 (6.94%)	42 / 738 (5.69%)
occurrences (all)	52	61	48
headache			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	40 / 736 (5.43%)	46 / 735 (6.26%)	52 / 738 (7.05%)
occurrences (all)	50	72	56
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	62 / 736 (8.42%)	54 / 735 (7.35%)	39 / 738 (5.28%)
occurrences (all)	81	62	44
nausea			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	33 / 736 (4.48%)	41 / 735 (5.58%)	32 / 738 (4.34%)
occurrences (all)	39	50	38
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	46 / 736 (6.25%)	25 / 735 (3.40%)	25 / 738 (3.39%)
occurrences (all)	49	29	25
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	57 / 736 (7.74%)	48 / 735 (6.53%)	34 / 738 (4.61%)
occurrences (all)	63	50	40
depression			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	36 / 736 (4.89%)	46 / 735 (6.26%)	31 / 738 (4.20%)
occurrences (all)	39	49	32
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	36 / 736 (4.89%)	33 / 735 (4.49%)	40 / 738 (5.42%)
occurrences (all)	38	35	50
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	78 / 736 (10.60%)	76 / 735 (10.34%)	60 / 738 (8.13%)
occurrences (all)	94	89	69
upper respiratory tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	39 / 736 (5.30%)	44 / 735 (5.99%)	46 / 738 (6.23%)
occurrences (all)	43	50	57
urinary tract infection			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed occurrences (all)	36 / 736 (4.89%) 53	32 / 735 (4.35%) 36	56 / 738 (7.59%) 70

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2015	Amendment (04): Protocol amended to specify -Co-administration of AZD3293 with food is now permitted. -Wording for permitted dose changes for cholinesterase inhibitors has been modified from "reductions" to "adjustments" to allow increases in dose if medically necessary. -Antipsychotic are no longer prohibited to allow treatment of patients if medically necessary.
30 June 2016	Amendment (07): - Changed the primary endpoint CDR-SB to ADAS-Cog13. -Updated potential risks to be consistent with the Investigator's Brochure (IB): Initiation of symptomatic treatments for patient progression (including acetylcholinesterase inhibitors [AChEI] and memantine) to now to be permitted at specific time intervals. -Broadened classes of applicable medications and added clinical judgment to Exclusion Criterion [26] about use of concomitant medications during study participation.
12 July 2017	Amendment (7.1): Added a fourth interim analysis with description. Clarified timing of third and fourth interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

An independent assessment concluded the trial was not likely to meet the primary endpoint upon completion and therefore, trial stopped for futility. Due to early termination of the study the planned population PK analysis was not performed.

Notes: