Clinical trial results:
A Phase III, Randomized, Placebo-Controlled, Parallel-Group, Double-Blind Clinical Trial to Study the Efficacy and Safety of MK-8931 (SCH 900931) in Subjects with Amnestic Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal AD)

Summary

EudraCT number	2015-002134-49
Trial protocol	FI ES BE DE AT PL IT FR
Global end of trial date	17 April 2018

Results information

Result version number	v1 (current)
This version publication date	19 June 2019
First version publication date	19 June 2019

Trial information

Trial identification

Sponsor protocol code	8931-019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01953601
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-8931-019

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 April 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study consists of two parts, Part 1 and Part 2. Part 1 assesses the efficacy and safety of verubecestat (MK-8931) compared with placebo administered for 104 weeks in the treatment of amnestic mild cognitive impairment (aMCI) due to Alzheimer's Disease (AD), also known as prodromal AD. Participants are randomized to receive placebo, or 12 mg or 40 mg verubecestat, once daily. The primary study hypothesis for Part 1 is that ≥1 verubecestat dose is superior to placebo with respect to the change from baseline in the Clinical Dementia Rating scale-Sum of Boxes (CDR-SB) score at 104 weeks. Participants completing Part 1 may choose to participate in Part 2, which is a long term double-blind extension to assess efficacy and safety of verubecestat administered for up to an additional 260 weeks. In Part 2, all participants receive either 12 mg or 40 mg verubecestat, once daily.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2013
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	Argentina: 35
Country: Number of subjects enrolled	Australia: 33
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Canada: 106
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	France: 44
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Italy: 98
Country: Number of subjects enrolled	Japan: 176
Country: Number of subjects enrolled	Korea, Republic of: 64
Country: Number of subjects enrolled	Netherlands: 15

Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Norway: 18
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Spain: 99
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United Kingdom: 81
Country: Number of subjects enrolled	United States: 572
Worldwide total number of subjects	1454
EEA total number of subjects	438

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)	243
From 65 to 84 years	1190
85 years and over	21

Subject disposition

Recruitment

Recruitment details:

N=1454 participants with prodromal Alzheimer's Disease (AD) were randomized, with N=1451 receiving study treatment.

Pre-assignment

Screening details:

This trial was conducted in 2 parts: a Base Study (Part 1), followed by an Extension Study (Part 2). Participants completing Part 1 had the option to continue to Part 2.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)

Arm description:

[Part 1] Verubecestat 12 mg once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive Verubecestat 12 mg once daily for an additional 260 weeks.

Arm type	Experimental
Investigational medicinal product name	Verubecestat 12 mg
Investigational medicinal product code	
Other name	MK-8931
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Verubecestat 12 mg oral tablet, given once daily.

Arm title	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)

Arm description:

[Part 1] Verubecestat 40 mg once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive Verubecestat 40 mg once daily for an additional 260 weeks.

Arm type	Experimental
Investigational medicinal product name	Verubecestat 40 mg
Investigational medicinal product code	
Other name	MK-8931
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Verubecestat 40 mg oral tablet, given once daily.

Arm title	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)

Arm description:

[Part 1] Placebo once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive Verubecestat 40 mg once daily for an additional 260 weeks.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching verubecestat, given once daily as an oral tablet.

Number of subjects in period 1	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Started	485	484	485
Treated	483	484	484
Completed	234	231	239
Not completed	251	253	246
Adverse event, serious fatal	2	-	3
Physician decision	3	7	4
Consent withdrawn by subject	32	23	22
Adverse event, non-fatal	24	37	15
Study terminated by sponsor	174	169	179
Non-compliance with study drug	-	3	1
Screen failure	1	-	1
Subject moved	2	2	1
Site discontinued study participation	2	-	-
Lost to follow-up	1	3	6
Discontinued due to caregiver withdrawal	7	8	10
Lack of efficacy	3	1	4

Period 2

Period 2 title	Part 2 (Extension Study)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)

Arm description:

[Part 1] Verubecestat 12 mg once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive verubecestat 12 mg once daily for an additional 260 weeks.

Arm type	Experimental
Investigational medicinal product name	Verubecestat 12 mg
Investigational medicinal product code	
Other name	MK-8931
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Verubecestat 12 mg oral tablet, given once daily.

Arm title	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)

Arm description:

[Part 1] Verubecestat 40 mg once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive verubecestat 40 mg once daily for an additional 260 weeks.

Arm type	Experimental
Investigational medicinal product name	Verubecestat 40 mg
Investigational medicinal product code	
Other name	MK-8931
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Verubecestat 40 mg oral tablet, given once daily.

Arm title	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)

Arm description:

[Part 1] Placebo once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive verubecestat 40 mg once daily for an additional 260 weeks.

Arm type	Experimental
Investigational medicinal product name	Verubecestat 40 mg
Investigational medicinal product code	
Other name	MK-8931
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Verubecestat 40 mg oral tablet, given once daily.

Number of subjects in period 2[1]	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Started	198	191	204
Treated	197	191	204
Completed	0	0	0
Not completed	198	191	204
Adverse event, serious fatal	-	3	-
Physician decision	2	-	2

Consent withdrawn by subject	5	4	2
Adverse event, non-fatal	1	1	10
Study terminated by sponsor	185	178	187
Subject moved	-	-	1
Site discontinued study participation	-	1	1
Lost to follow-up	2	1	1
Discontinued due to caregiver withdrawal	1	3	-
Lack of efficacy	2	-	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Number completing Part 1, volunteering for Part 2.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)
Reporting group description:	
[Part 1] Verubecestat 12 mg once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive Verubecestat 12 mg once daily for an additional 260 weeks.	
Reporting group title	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)
Reporting group description:	
[Part 1] Verubecestat 40 mg once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive Verubecestat 40 mg once daily for an additional 260 weeks.	
Reporting group title	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Reporting group description:	
[Part 1] Placebo once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive Verubecestat 40 mg once daily for an additional 260 weeks.	

Reporting group values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects	485	484	485
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	85	78	80
From 65-84 years	392	398	400
85 years and over	8	8	5
Age Continuous			
Units: Years			
arithmetic mean	71.7	71.0	71.6
standard deviation	± 7.1	± 7.4	± 7.1
Sex: Female, Male			
Units: Subjects			
Female	229	244	213
Male	256	240	272
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	2
Asian	79	85	84
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	3	6
White	397	392	391
More than one race	2	1	0

Unknown or Not Reported	2	3	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	28	29	29
Not Hispanic or Latino	441	439	441
Unknown or Not Reported	16	16	15
Geographic Region Units: Subjects			
United States / Canada	226	224	226
Japan	57	60	59
Europe / Australia / New Zealand	163	163	161
Other	37	37	38
Excluded (participant not treated)	2	0	1
APOE4 Genotype			
Apolipoprotein E (APOE) genotype is the strongest genetic predictor of risk for developing AD. The number of participants testing positive or negative for the APOE4 allele at baseline is presented.			
Units: Subjects			
Negative	155	146	148
Positive	328	337	335
Missing	0	1	1
Excluded (participant not treated)	2	0	1
Baseline Use of Vitamin E			
The number of participants receiving Vitamin E (> or ≤ 400 International Units [IU] / day; or no use) is presented.			
Units: Subjects			
No Use	351	372	355
≤400 IU / day	123	100	120
>400 IU / day	9	12	9
Excluded (participant not treated)	2	0	1
Background Alzheimer's Disease (AD) Treatment			
The number of participants receiving acetylcholinesterase inhibitors (AChEI) and/or memantine (or no background AD treatment) is presented.			
Units: Subjects			
Use of AChEI alone	182	191	180
Use of memantine alone	9	8	8
Use of AChEI and memantine	31	26	34
No use of AChEI or memantine	261	259	262
Excluded (participant not treated)	2	0	1
Mini-Mental State Examination (MMSE) Score			
The MMSE is a cognitive assessment of 5 domains (orientation; attention; memory; language; constructional praxis), with 11 questions scored based on number of correct responses. Depending on the question, scores range from 0 (no correct response) to either 1 (4 questions), 2 (1 question), 3 (3 questions), or 5 (3 questions). Scores for each question sum to a total MMSE score (range: 0-30); lower scores indicate worse cognitive performance. Participants are stratified by MMSE score (≥24-26 or ≥27) to ensure a representative population by AD severity across study arms.			
Units: Subjects			
MMSE ≥27	212	211	214
MMSE ≥24-26	270	271	270
Missing	1	2	0
Excluded (participant not treated)	2	0	1

Clinical Dementia Rating Sum of Boxes (CDR-SB) Score			
The CDR-SB score is a clinical rating of global cognitive function, comprised of 6 domains: memory; orientation; judgment and problem solving; community affairs; home and hobbies; and personal care. For each domain, the degree of impairment is assessed by a semi-structured interview of the participant as well as the participant's caregiver. For each domain, potential scores range from 0 (no impairment) to 3 (severe impairment). Individual domain scores are summed to a total CDR-SB score (range: 0-18). Higher scores indicate more severe cognitive impairment. (N= 465, 458, 469)			
Units: Score on a Scale			
arithmetic mean	2.7	2.7	2.6
standard deviation	± 1.3	± 1.3	± 1.2
Composite Cognition Score-3 Domain (CCS-3D)			
CCS-3D is composed of individual cognitive tests, grouped into 3 domains: 1) episodic memory; 2) executive function; and 3) attention/processing speed. For each test, a z-score (Z) is calculated at each time point [Z = (observed value - study population mean at baseline) / study population standard deviation at baseline]. Individual Zs are first combined into domain-specific Zs, and then into a composite Z, (i.e. CCS-3D). In theory, 99.9% of CCS-3D will be ± 3; more positive CCS-3D indicate greater cognitive impairment relative to the total study population at baseline. (N= 441, 424, 440)			
Units: Z-score			
arithmetic mean	0.0	0.0	-0.1
standard deviation	± 1.0	± 1.0	± 1.0
Total Hippocampal Volume (THV)			
THV was measured by volumetric magnetic resonance imaging (vMRI). (N= 168, 181, 191)			
Units: µL			
arithmetic mean	6448.4	6468.5	6435.4
standard deviation	± 1107.1	± 1105.8	± 987.2
[18F]Flutemetamol Positron Emission Tomography (PET) Standard Uptake Value Ratio (SUVR)			
[18F]Flutemetamol PET SUVR measures brain cortical amyloid load. The PET tracer [18F]Flutemetamol was given intravenously (IV). After 90 minutes uptake, participants were scanned for 20 minutes. Using the PET scan images, SUVRs, the ratio of tracer signal in a specific region compared to a reference region (RR; subcortical white matter) are calculated for brain regions of interest (ROIs). SUVRs from a selected set of brain regions are averaged to compute a composite SUVR. Higher composite SUVR values indicate increased amyloid load in selected brain regions. (N= 63, 59, 65)			
Units: Standard Uptake Value Ratio (SUVR)			
arithmetic mean	0.86	0.87	0.85
standard deviation	± 0.07	± 0.07	± 0.06
AD Cooperative Study-Activities of Daily Living, Mild Cognitive Impairment (ADCS-ADL MCI) Score			
The ADCS-ADL MCI is an 18-item assessment of recent, observed performance of activities of daily living administered to participants' trial partners in an interview format. For the 18 items, scores range from 0 (no independence) to (depending on the item) either 2 (5 items), 3 (9 items), or 4 (4 items), with higher scores indicating greater independence in activity performance. Scores from individual items are summed for a total ADCS-ADL score (range: 0-53). Lower scores indicate less independence in activity performance and, as a result, greater AD severity. (N= 469, 462, 472)			
Units: Score on a Scale			
arithmetic mean	42.2	43.1	42.8
standard deviation	± 5.9	± 5.4	± 5.9
Cerebrospinal Fluid (CSF) Total Tau Concentration			
Total Tau concentration in the CSF was monitored as a measure of brain tau pathology. (N= 5, 6, 6)			
Units: pg/mL			
arithmetic mean	203.8	159.3	243.5
standard deviation	± 129.1	± 79.0	± 97.0

Reporting group values	Total		

Number of subjects	1454		
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)	243		
From 65-84 years	1190		
85 years and over	21		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	686		
Male	768		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2		
Asian	248		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	14		
White	1180		
More than one race	3		
Unknown or Not Reported	7		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	86		
Not Hispanic or Latino	1321		
Unknown or Not Reported	47		
Geographic Region Units: Subjects			
United States / Canada	676		
Japan	176		
Europe / Australia / New Zealand	487		
Other	112		
Excluded (participant not treated)	3		
APOE4 Genotype			
Apolipoprotein E (APOE) genotype is the strongest genetic predictor of risk for developing AD. The number of participants testing positive or negative for the APOE4 allele at baseline is presented.			
Units: Subjects			
Negative	449		
Positive	1000		
Missing	2		
Excluded (participant not treated)	3		
Baseline Use of Vitamin E			

The number of participants receiving Vitamin E (> or ≤ 400 International Units [IU] / day; or no use) is presented.			
Units: Subjects			
No Use	1078		
≤400 IU / day	343		
>400 IU / day	30		
Excluded (participant not treated)	3		
Background Alzheimer's Disease (AD) Treatment			
The number of participants receiving acetylcholinesterase inhibitors (AChEI) and/or memantine (or no background AD treatment) is presented.			
Units: Subjects			
Use of AChEI alone	553		
Use of memantine alone	25		
Use of AChEI and memantine	91		
No use of AChEI or memantine	782		
Excluded (participant not treated)	3		
Mini-Mental State Examination (MMSE) Score			
The MMSE is a cognitive assessment of 5 domains (orientation; attention; memory; language; constructional praxis), with 11 questions scored based on number of correct responses. Depending on the question, scores range from 0 (no correct response) to either 1 (4 questions), 2 (1 question), 3 (3 questions), or 5 (3 questions). Scores for each question sum to a total MMSE score (range: 0-30); lower scores indicate worse cognitive performance. Participants are stratified by MMSE score (≥24-26 or ≥27) to ensure a representative population by AD severity across study arms.			
Units: Subjects			
MMSE ≥27	637		
MMSE ≥24-26	811		
Missing	3		
Excluded (participant not treated)	3		
Clinical Dementia Rating Sum of Boxes (CDR-SB) Score			
The CDR-SB score is a clinical rating of global cognitive function, comprised of 6 domains: memory; orientation; judgment and problem solving; community affairs; home and hobbies; and personal care. For each domain, the degree of impairment is assessed by a semi-structured interview of the participant as well as the participant's caregiver. For each domain, potential scores range from 0 (no impairment) to 3 (severe impairment). Individual domain scores are summed to a total CDR-SB score (range: 0-18). Higher scores indicate more severe cognitive impairment. (N= 465, 458, 469)			
Units: Score on a Scale			
arithmetic mean			
standard deviation	-		
Composite Cognition Score-3 Domain (CCS-3D)			
CCS-3D is composed of individual cognitive tests, grouped into 3 domains: 1) episodic memory; 2) executive function; and 3) attention/processing speed. For each test, a z-score (Z) is calculated at each time point [Z = (observed value - study population mean at baseline) / study population standard deviation at baseline]. Individual Zs are first combined into domain-specific Zs, and then into a composite Z, (i.e. CCS-3D). In theory, 99.9% of CCS-3D will be ± 3; more positive CCS-3D indicate greater cognitive impairment relative to the total study population at baseline. (N= 441, 424, 440)			
Units: Z-score			
arithmetic mean			
standard deviation	-		
Total Hippocampal Volume (THV)			
THV was measured by volumetric magnetic resonance imaging (vMRI). (N= 168, 181, 191)			
Units: µL			
arithmetic mean			
standard deviation	-		
[18F]Flutemetamol Positron Emission			

Tomography (PET) Standard Uptake Value Ratio (SUVR)			
[18F]Flutemetamol PET SUVR measures brain cortical amyloid load. The PET tracer [18F]Flutemetamol was given intravenously (IV). After 90 minutes uptake, participants were scanned for 20 minutes. Using the PET scan images, SUVRs, the ratio of tracer signal in a specific region compared to a reference region (RR; subcortical white matter) are calculated for brain regions of interest (ROIs). SUVRs from a selected set of brain regions are averaged to compute a composite SUVR. Higher composite SUVR values indicate increased amyloid load in selected brain regions. (N= 63, 59, 65)			
Units: Standard Uptake Value Ratio (SUVR) arithmetic mean standard deviation	- -		
AD Cooperative Study-Activities of Daily Living, Mild Cognitive Impairment (ADCS-ADL MCI) Score			
The ADCS-ADL MCI is an 18-item assessment of recent, observed performance of activities of daily living administered to participants' trial partners in an interview format. For the 18 items, scores range from 0 (no independence) to (depending on the item) either 2 (5 items), 3 (9 items), or 4 (4 items), with higher scores indicating greater independence in activity performance. Scores from individual items are summed for a total ADCS-ADL score (range: 0-53). Lower scores indicate less independence in activity performance and, as a result, greater AD severity. (N= 469, 462, 472)			
Units: Score on a Scale arithmetic mean standard deviation	- -		
Cerebrospinal Fluid (CSF) Total Tau Concentration			
Total Tau concentration in the CSF was monitored as a measure of brain tau pathology. (N= 5, 6, 6)			
Units: pg/mL arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)
Reporting group description:	
[Part 1] Verubecestat 12 mg once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive Verubecestat 12 mg once daily for an additional 260 weeks.	

Reporting group title	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)
Reporting group description:	
[Part 1] Verubecestat 40 mg once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive Verubecestat 40 mg once daily for an additional 260 weeks.	

Reporting group title	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Reporting group description:	
[Part 1] Placebo once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive Verubecestat 40 mg once daily for an additional 260 weeks.	

Reporting group title	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)
Reporting group description:	
[Part 1] Verubecestat 12 mg once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive verubecestat 12 mg once daily for an additional 260 weeks.	

Reporting group title	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)
Reporting group description:	
[Part 1] Verubecestat 40 mg once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive verubecestat 40 mg once daily for an additional 260 weeks.	

Reporting group title	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Reporting group description:	
[Part 1] Placebo once daily for 104 weeks in Part 1 (Base Study). [Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive verubecestat 40 mg once daily for an additional 260 weeks.	

Primary: Part 1 (Base Study). Least Squares Mean (LSM) Change from Baseline in Clinical Dementia Rating Sum of Boxes (CDR-SB) Score at Week 104

End point title	Part 1 (Base Study). Least Squares Mean (LSM) Change from Baseline in Clinical Dementia Rating Sum of Boxes (CDR-SB) Score at Week 104
End point description:	
LSM change from baseline at week 104 was assessed for CDR-SB score, a clinical rating of global cognitive function, comprised of 6 domains: memory; orientation; judgment and problem solving; community affairs; home and hobbies; and personal care. For each domain, the degree of impairment is assessed by a semi-structured interview of the participant as well as the participant's caregiver. For each domain, potential scores range from 0 (no impairment) to 3 (severe impairment). Individual domain scores are summed to a total CDR-SB score (range: 0-18). Higher scores indicate more severe cognitive impairment. Further, increases in cognitive impairment would be reflected by increases in CDR-SB score. Analysis Population: Includes all participants receiving ≥1 dose of study treatment in Part 1 who: 1) had both a pre-dose baseline and ≥1 within-analysis-window, post-dose CDR-SB observation; and 2) tested positive for cortical amyloid load by PET.	

End point type	Primary
End point timeframe:	
Baseline and Week 104 in Part 1	

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	465	458	469	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	1.6 (1.4 to 1.9)	2.0 (1.8 to 2.3)	1.6 (1.3 to 1.8)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean (LSM)
Statistical analysis description: Difference in LSM = Arm A - Arm C	
Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	934
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6734
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	0.1
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-0.3
upper limit	0.4

Statistical analysis title	Difference in Least Squares Means (LSM)
Statistical analysis description: Difference in LSM = Arm B - Arm C	
Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	927
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0141
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Means (LSM)
Point estimate	0.4

Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	0
upper limit	0.8

Primary: Part 2 (Extension Study). Mean Change from Baseline in Clinical Dementia Rating Sum of Boxes (CDR-SB) Score at Week 130

End point title	Part 2 (Extension Study). Mean Change from Baseline in Clinical Dementia Rating Sum of Boxes (CDR-SB) Score at Week 130[1]

End point description:

Mean change from baseline at week 130 was assessed for CDR-SB score, a clinical rating of global cognitive function, comprised of 6 domains: memory; orientation; judgment and problem solving; community affairs; home and hobbies; and personal care. For each domain, degree of impairment is assessed by a semi-structured interview of the participant as well as their caregiver. For each domain, scores range from 0 (no impairment) to 3 (severe impairment). Individual domain scores are summed to a total CDR-SB score (range: 0-18). Higher scores indicate more severe cognitive impairment. Further, increases in cognitive impairment would be reflected by increases in CDR-SB score. Per protocol, baseline refers to the Part 1 baseline measurement. Analysis Population: All participants continuing to Part 2, with: 1) both a pre-dose baseline and ≥1 within-analysis-window, post-dose CDR-SB observation; 2) a positive test for cortical amyloid load by PET; and 3) a CDR-SB observation at week 130.

End point type	Primary

End point timeframe:

Baseline and Week 130 (i.e., Week 26 of Part 2)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not performed due to early trial termination.

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	124	
Units: Score on a Scale				
arithmetic mean (standard deviation)	2.0 (± 2.5)	1.9 (± 2.2)	1.5 (± 2.1)	

Statistical analyses

No statistical analyses for this end point

Primary: Part 1 (Base Study). Percentage of Participants Who Experienced ≥1 Adverse Event (AE)

End point title	Part 1 (Base Study). Percentage of Participants Who Experienced ≥1 Adverse Event (AE)

End point description:

The percentage of participants experiencing an AE in Part 1 was assessed. An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE

can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor's product is also an AE. Analysis Population: All randomized participants in Part 1, receiving ≥1 dose of study treatment.

End point type	Primary

End point timeframe:

Up to Week 106 (up to 2 weeks following cessation of study treatment in Part 1)

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	483	484	484	
Units: Percentage of Participants				
number (not applicable)	91.3	92.1	87.0	

Statistical analyses

Statistical analysis title	Difference in % vs Placebo
Statistical analysis description: Difference in % = Arm A - Arm C	
Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	967
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % vs Placebo
Point estimate	4.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	8.31

Statistical analysis title	Difference in % vs Placebo
Statistical analysis description: Difference in % = Arm B - Arm C	
Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)

Number of subjects included in analysis	968
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % vs Placebo
Point estimate	5.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	9.09

Primary: Part 1 (Base Study). Percentage of Participants Who Discontinued From Study Drug Due to an Adverse Event (AE)

End point title	Part 1 (Base Study). Percentage of Participants Who Discontinued From Study Drug Due to an Adverse Event (AE)

End point description:

The percentage of participants who discontinued from study drug due to an AE in Part 1 was assessed. An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor's product is also an AE. Analysis Population: All randomized participants in Part 1, receiving ≥1 dose of study treatment.

End point type	Primary

End point timeframe:

Up to Week 104 in Part 1

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	483	484	484	
Units: Percentage of Participants				
number (not applicable)	6.6	10.1	4.5	

Statistical analyses

Statistical analysis title	Difference in % vs Placebo

Statistical analysis description:

Difference in % = Arm B - Arm C

Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)

Number of subjects included in analysis	968
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % vs Placebo
Point estimate	5.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.35
upper limit	8.99

Statistical analysis title	Difference in % vs Placebo
Statistical analysis description:	
Difference in % = Arm A - Arm C	
Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	967
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % vs Placebo
Point estimate	2.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	5.1

Primary: Part 2 (Extension Study). Percentage of Participants Who Experienced ≥1 Adverse Event (AE)

End point title	Part 2 (Extension Study). Percentage of Participants Who Experienced ≥1 Adverse Event (AE)

End point description:

The percentage of participants experiencing an AE in Part 2 was assessed. An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor’s product is also an AE. Analysis Population: All randomized participants continuing to Part 2, receiving ≥1 dose of trial treatment in Part 2. For included participants, the data reflect AEs occurring in Part 2 only.

End point type	Primary

End point timeframe:

From Week 104 (start of treatment in Part 2) up to Week 210 (up to 2 weeks following cessation of study treatment in Part 2)

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197	191	204	
Units: Percentage of Participants				
number (not applicable)	59.4	55.5	66.2	

Statistical analyses

Statistical analysis title	Difference in % vs Placebo
Statistical analysis description: Difference in % = Arm A - Arm C	
Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % vs Placebo
Point estimate	-6.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.16
upper limit	2.68

Statistical analysis title	Difference in % vs Placebo
Statistical analysis description: Difference in % = Arm B - Arm C	
Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % vs Placebo
Point estimate	-10.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.16
upper limit	-1.04

Primary: Part 2 (Extension Study). Percentage of Participants Who Discontinued From Study Drug Due to an Adverse Event (AE)

End point title	Part 2 (Extension Study). Percentage of Participants Who Discontinued From Study Drug Due to an Adverse Event (AE)

End point description:

The percentage of participants who discontinued from study drug due to an AE in Part 2 was assessed. An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor's product is also an AE. Analysis Population: All randomized participants continuing to Part 2, receiving ≥1 dose of trial treatment in Part 2. For included participants, the data reflect discontinuations occurring in Part 2 only.

End point type	Primary

End point timeframe:

From Week 104 (start of treatment in Part 2) up to Week 208 (i.e., up to Week 104 in Part 2)

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197	191	204	
Units: Percentage of Participants				
number (not applicable)	1.0	1.0	3.4	

Statistical analyses

Statistical analysis title	Difference in % vs Placebo
Statistical analysis description:	
Difference in % = Arm A - Arm C	
Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % vs Placebo
Point estimate	-2.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.03
upper limit	0.61

Statistical analysis title	Difference in % vs Placebo
Statistical analysis description:	
Difference in % = Arm B - Arm C	
Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C.

	Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % vs Placebo
Point estimate	-2.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.01
upper limit	0.71

Secondary: Part 1 (Base Study). Event-Rate per 100 Participant Years for Progression to a Clinical Diagnosis of Probable AD Dementia

End point title	Part 1 (Base Study). Event-Rate per 100 Participant Years for Progression to a Clinical Diagnosis of Probable AD Dementia

End point description:

The event-rate per 100 participant-years for progression to a clinical diagnosis of probable AD dementia was calculated. Adjudication of a potential case was triggered if either: 1) in the investigator's own expert judgment, they think the participant may have progressed to dementia and/or 2) the participant's CDR-SB score is ≥2 points higher compared to baseline. Cases of progression to probable AD dementia confirmed by an external adjudication committee were counted as events in the analysis. The event-rate was calculated as the number of events divided by total follow-up time (participant-years) x 100; unit of measure is event-rate / 100 participant-years. Analysis Population: Includes all participants receiving ≥1 dose of study treatment in Part 1 who tested positive for cortical amyloid load

End point type	Secondary

End point timeframe:

Up to Week 104 in Part 1

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	480	481	481	
Units: Event-Rate / 100 Participant-Years				
number (not applicable)	24.5	25.5	19.3	

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)

Statistical analysis description:

HR = Arm A / Arm C

Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)

Number of subjects included in analysis	961
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0222
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.301
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	1.005
upper limit	1.684

Statistical analysis title	Hazard Ratio (HR)
Statistical analysis description:	
HR = Arm B / Arm C	
Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	962
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.005
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.382
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	1.067
upper limit	1.79

Secondary: Part 1 (Base Study). Estimated Least Squares Mean Difference between the Last (Week 104) and First (Week 13) Post-dose CDR-SB Assessment

End point title	Part 1 (Base Study). Estimated Least Squares Mean Difference between the Last (Week 104) and First (Week 13) Post-dose CDR-SB Assessment

End point description:

LSM difference between weeks 104 and 13 was estimated for CDR-SB score, a clinical rating of global cognitive function, comprised of 6 domains: memory; orientation; judgment / problem solving; community affairs; home / hobbies; and personal care. For each domain, degree of impairment is scored by a semi-structured interview of the participant and the participant's caregiver (domain score range: 0 [no impairment] to 3 [severe impairment]). Domain scores sum to a total CDR-SB score (range: 0-18); higher scores indicate more severe cognitive impairment. Further, increased cognitive impairment is reflected by higher CDR-SB scores; larger differences between week 104 and week 13 scores indicates accelerated AD progression. Analysis Population: Includes all participants receiving ≥1 dose of study treatment in Part 1 who: 1) had both a pre-dose baseline and ≥1 within-analysis-window, post-dose CDR-SB observation; and 2) tested positive for cortical amyloid load by PET.

End point type	Secondary

End point timeframe:

Week 13 and Week 104 in Part 1

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	465	458	469	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	1.5 (1.3 to 1.7)	1.8 (1.5 to 2.0)	1.5 (1.3 to 1.7)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean (LSM)
Statistical analysis description: Difference in LSM = Arm A - Arm C	
Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	934
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9109
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	0
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-0.3
upper limit	0.4

Statistical analysis title	Difference in Least Squares Mean (LSM)
Statistical analysis description: Difference in LSM = Arm B - Arm C	
Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	927
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0824
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	0.3

Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-0.1
upper limit	0.7

Secondary: Part 1 (Base Study). Least Squares Mean Change from Baseline in the 3-Domain Composite Cognition Score (CCS-3D) at Week 104

End point title	Part 1 (Base Study). Least Squares Mean Change from Baseline in the 3-Domain Composite Cognition Score (CCS-3D) at Week 104

End point description:

CCS-3D is composed of individual cognitive tests, grouped into 3 domains: 1) episodic memory; 2) executive function; and 3) attention/processing speed. For each cognitive test, a z-score (Z) is calculated at each time point [Z = (observed value - study population mean at baseline) / study population standard deviation at baseline]. These individual Zs are first combined into domain-specific Zs, and then into a composite Z, (i.e. CCS-3D). Theoretically, 99.9% of CCS-3D will be ± 3; more positive CCS-3D indicate greater cognitive impairment relative to the total study population at baseline. Further, negative changes in CCS-3D over time indicate improved cognition relative to the total study population at baseline. Analysis Population: Includes all participants receiving ≥1 dose of study treatment who: 1) had both a pre-dose baseline and ≥1 within-analysis-window, post-dose CCS-3D observation; and 2) tested positive for cortical amyloid load by PET.

End point type	Secondary

End point timeframe:

Baseline and Week 104 in Part 1

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	441	424	440	
Units: Z-score				
least squares mean (confidence interval 95%)	0.8 (0.7 to 0.9)	0.8 (0.7 to 0.9)	0.8 (0.7 to 0.9)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean (LSM)

Statistical analysis description:

Difference in LSM = Arm A - Arm C

Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)

Number of subjects included in analysis	881
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.951
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	0
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Statistical analysis title	Difference in Least Squares Mean (LSM)
Statistical analysis description:	
Difference in LSM = Arm B - Arm C	
Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	864
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9392
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	0
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Secondary: Part 1 (Base Study). Least Squares Mean Percent Change from Baseline in Total Hippocampal Volume (THV) at Week 104

End point title	Part 1 (Base Study). Least Squares Mean Percent Change from Baseline in Total Hippocampal Volume (THV) at Week 104

End point description:

Least squares mean percent change from baseline at week 104 was calculated for THV as measured by volumetric magnetic resonance imaging (vMRI). Negative percent changes from baseline indicate decreases in THV (i.e. increased hippocampal atrophy). Analysis Population: Includes all participants receiving ≥1 dose of study treatment who: 1) had both a pre-dose baseline and ≥1 within-analysis-window, post-dose THV observation; and 2) tested positive for cortical amyloid load by PET.

End point type	Secondary

End point timeframe:

Baseline and Week 104 in Part 1

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	168	181	191	
Units: Percent Change				
least squares mean (confidence interval 95%)	-6.5 (-6.9 to -6.2)	-6.7 (-7.1 to -6.3)	-6.1 (-6.5 to -5.7)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean (LSM)
Statistical analysis description: Difference in LSM = Arm A - Arm C	
Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1133
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	-0.4
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-1
upper limit	0.2

Statistical analysis title	Difference in Least Squares Mean (LSM)
Statistical analysis description: Difference in LSM = Arm B - Arm C	
Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.031
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	-0.6
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-1.2
upper limit	0

Secondary: Part 1 (Base Study). Least Squares Mean Change from Baseline in Composite Cortical Amyloid Standard Uptake Value Ratio (SUVR) Assessed with Amyloid Tracer [18F]Flutemetamol using Positron Emission Tomography (PET) Imaging at Week 104

End point title	Part 1 (Base Study). Least Squares Mean Change from Baseline in Composite Cortical Amyloid Standard Uptake Value Ratio (SUVR) Assessed with Amyloid Tracer [18F]Flutemetamol using Positron Emission Tomography (PET) Imaging at Week 104

End point description:

[18F]Flutemetamol PET SUVR measures brain cortical amyloid load. The PET tracer [18F]Flutemetamol was given intravenously (IV). After 90 minutes, participants were scanned for 20 minutes. Using the PET scan images, SUVRs, the ratio of tracer signal in a specific region compared to a reference region (RR; subcortical white matter) are calculated for brain regions of interest (ROIs). SUVRs from a selected set of brain regions are averaged to compute a composite SUVR. Higher composite SUVR values indicate increased amyloid load in selected brain regions, with negative changes in composite cortical SUVR over time indicating decreases in brain amyloid load. Analysis Population: Includes all participants receiving ≥1 dose of study treatment who: 1) had both a pre-dose baseline and ≥1 within-analysis-window, post-dose SUVR observation; and 2) tested positive for cortical amyloid load by PET.

End point type	Secondary

End point timeframe:

Baseline and Week 104 in Part 1

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	59	65	
Units: Standard Uptake Value Ratio (SUVR)				
least squares mean (confidence interval 95%)	-0.03 (-0.04 to -0.03)	-0.04 (-0.05 to -0.04)	0.02 (0.02 to 0.03)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean (LSM)

Statistical analysis description:

Difference in LSM = Arm A - Arm C

Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	-0.05

Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-0.06
upper limit	-0.04

Statistical analysis title	Difference in Least Squares Mean (LSM)
Statistical analysis description: Difference in LSM = Arm B - Arm C	
Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	-0.06
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-0.07
upper limit	-0.05

Secondary: Part 1 (Base Study). Least Squares Mean Change from Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL MCI) Score at Week 104

End point title	Part 1 (Base Study). Least Squares Mean Change from Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL MCI) Score at Week 104

End point description:

Least squares mean change from baseline at week 104 was assessed for the ADCS-ADL MCI score. The ADCS-ADL MCI is an 18-item assessment of recent, observed performance of activities of daily living administered to participants' trial partners in an interview format. For the 18 items, scores range from 0 (no independence) to (depending on the item) either 2 (5 items), 3 (9 items), or 4 (4 items), with higher scores indicating greater independence in activity performance. Scores from individual items sum to a total ADCS-ADL score (range: 0-53). Lower scores indicate less independence in activity performance and, as a result, greater AD severity. Further, increases in AD severity over time would be reflected by decreases in ADCS-ADL score. Analysis Population: Includes all participants receiving ≥1 dose of study treatment who: 1) had both a pre-dose baseline and ≥1 within-analysis-window, post-dose ADCS-ADL MCI observation; and 2) tested positive for cortical amyloid load by PET.

End point type	Secondary

End point timeframe:

Baseline and Week 104 in Part 1

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	469	462	472	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	-5.2 (-6.1 to -4.3)	-5.8 (-6.8 to -4.8)	-4.1 (-5.0 to -3.3)	

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean (LSM)
Statistical analysis description: Difference in LSM = Arm A - Arm C	
Comparison groups	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.096
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	-1
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-2.4
upper limit	0.4

Statistical analysis title	Difference in Least Squares Mean (LSM)
Statistical analysis description: Difference in LSM = Arm B - Arm C	
Comparison groups	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2) v Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)
Number of subjects included in analysis	934
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.011
Method	Longitudinal ANCOVA
Parameter estimate	Difference in Least Squares Mean (LSM)
Point estimate	-1.7
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	-3.2
upper limit	-0.2

Secondary: Part 1 (Base Study). Least Squares Mean Percent Change from Baseline in Cerebrospinal Fluid (CSF) Total Tau Concentration at Week 104

End point title	Part 1 (Base Study). Least Squares Mean Percent Change from Baseline in Cerebrospinal Fluid (CSF) Total Tau Concentration at Week 104

End point description:

Least squares mean percent change from baseline at week 104 was calculated for Total Tau concentration in CSF, a measure of brain tau pathology. Per protocol, CSF Total Tau concentration was analyzed as part of a substudy in Part 1, with testing occurring only at select trial sites. Analysis Population: Includes all participants receiving ≥1 dose of study treatment who: 1) had both a pre-dose baseline and ≥1 within-analysis-window, post-dose observation for CSF Total Tau concentration; and 2) tested positive for cortical amyloid load by PET. CSF Total Tau concentration was analyzed at select trial sites as a Part 1 substudy.

End point type	Secondary

End point timeframe:

Baseline and Week 104 in Part 1

End point values	Arm A. Verubecestat 12 mg (Part 1); 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 1); 40 mg (Part 2)	Arm C. Placebo (Part 1); Verubecestat 40 mg (Part 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: Percent Change				
arithmetic mean (standard deviation)	33.2 (± 44.3)	42.8 (± 39.7)	10.2 (± 27.9)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

[Part 1]: Up to Week 106 of Part 1 (up to 2 weeks following cessation of study treatment in Part 1); [Part 2]: From Week 104 (start of treatment in Part 2) up to Week 210 (up to 2 weeks following cessation of study treatment in Part 2).

Adverse event reporting additional description:

[Part 1] all randomized participants receiving ≥1 dose of treatment. [Part 2] all participants continuing to Part 2, receiving ≥1 dose of treatment in Part 2. For Part 2 arms, only AEs occurring in Part 2 are reported. For serious AEs determined to be causally related to treatment, this reflects assessment of a blinded investigator during trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Arm A. Verubecestat 12 mg (Part 1)

Reporting group description:

[Part 1] Verubecestat 12 mg once daily for 104 weeks in Part 1 (Base Study).

Reporting group title	Arm B. Verubecestat 40 mg (Part 1)

Reporting group description:

[Part 1] Verubecestat 40 mg once daily for 104 weeks in Part 1 (Base Study).

Reporting group title	Arm C. Placebo (Part 1)

Reporting group description:

[Part 1] Placebo once daily for 104 weeks in Part 1 (Base Study).

Reporting group title	Arm A. Verubecestat 12 mg (Part 2)

Reporting group description:

[Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive verubecestat 12 mg once daily for an additional 260 weeks.

Reporting group title	Arm B. Verubecestat 40 mg (Part 2)

Reporting group description:

[Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive verubecestat 40 mg once daily for an additional 260 weeks.

Reporting group title	Arm C. Verubecestat 40 mg (Part 2)

Reporting group description:

[Part 2] Participants completing Part 1 and continuing to Part 2 (Extension Study) receive verubecestat 40 mg once daily for an additional 260 weeks.

Serious adverse events	Arm A. Verubecestat 12 mg (Part 1)	Arm B. Verubecestat 40 mg (Part 1)	Arm C. Placebo (Part 1)
Total subjects affected by serious adverse events			
subjects affected / exposed	124 / 483 (25.67%)	101 / 484 (20.87%)	96 / 484 (19.83%)
number of deaths (all causes)	3	1	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of prostate			
subjects affected / exposed	0 / 483 (0.00%)	2 / 484 (0.41%)	0 / 484 (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
Atypical fibroxanthoma			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Basal cell carcinoma			
subjects affected / exposed	13 / 483 (2.69%)	8 / 484 (1.65%)	6 / 484 (1.24%)
occurrences causally related to treatment / all	0 / 14	0 / 10	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Bladder neoplasm			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Bowen's disease			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer metastatic			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer recurrent			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Carcinoma in situ of breast ductal			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Cervical cancer			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Colonic tubular adenoma			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Endometrial cancer			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Follicular thyroid cancer			

subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Gastric adenoma			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Gastric cancer			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Lentigo melanoma			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip basal cell carcinoma			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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 metastatic			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Malignant melanoma			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Malignant melanoma in situ			

subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Melanoma			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Melanoma in situ			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic gastric cancer			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Multiple myeloma			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodular basal cell carcinoma			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreas cancer			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Prostate cancer			

subjects affected / exposed	3 / 483 (0.62%)	2 / 484 (0.41%)	5 / 484 (1.03%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer recurrent			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
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 carcinoma			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Skin cancer			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
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 carcinoma			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	3 / 483 (0.62%)	2 / 484 (0.41%)	2 / 484 (0.41%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of head and neck			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 of skin			
subjects affected / exposed	5 / 483 (1.04%)	3 / 484 (0.62%)	5 / 484 (1.03%)
occurrences causally related to treatment / all	1 / 6	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin in situ			
subjects affected / exposed	1 / 483 (0.21%)	2 / 484 (0.41%)	0 / 484 (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
Squamous cell carcinoma of skin well differentiated			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 of the nasal cavity			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Superficial basal cell carcinoma			
subjects affected / exposed	3 / 483 (0.62%)	0 / 484 (0.00%)	3 / 484 (0.62%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Throat cancer			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Urothelial carcinoma			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	2 / 484 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial stenosis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Hypertensive episode			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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 obliterative arteriopathy			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Aortic stenosis			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Acute chest pain			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Chest pain			
subjects affected / exposed	3 / 483 (0.62%)	2 / 484 (0.41%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain aggravated			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pressure			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Fever			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Fever of unknown origin			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Gait abnormal			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Non-cardiac chest pain			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
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			
Hypersensitivity reaction			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Bartholin's cyst			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Benign prostatic hypertrophy			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystocele			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urogenital prolapse			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease exacerbation			

subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Collapse of lung			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Epistaxis			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Pharyngeal haematoma			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Pleural effusion			
subjects affected / exposed	0 / 483 (0.00%)	2 / 484 (0.41%)	0 / 484 (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
Pulmonary embolism			
subjects affected / exposed	2 / 483 (0.41%)	1 / 484 (0.21%)	0 / 484 (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
Pulmonary oedema			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Acute mania			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Agitation			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Anxiety			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusion aggravated			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	3 / 483 (0.62%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Disorientation			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychosis aggravated			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Psychotic disorder			

subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Psychotic episode			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Somatisation disorder			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Suicidal ideation			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Unsuccessful suicide			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Acute delirium			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Creatinine increased			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Faecal occult blood			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic specific antigen increased			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	0 / 484 (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
Troponin increased			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol intoxication			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Arm fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Bimalleolar fracture			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Bruise of head			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Chronic subdural haematoma			

subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Fall			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	3 / 484 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Finger injury			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Fracture of intertrochanteric section of femur, closed			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Fractured mandible			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 fracture			
subjects affected / exposed	2 / 483 (0.41%)	0 / 484 (0.00%)	0 / 484 (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
Humerus fracture			
subjects affected / exposed	1 / 483 (0.21%)	2 / 484 (0.41%)	2 / 484 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint ligament rupture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 spine compression fracture			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Multiple fractures			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Near drowning			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Olecranon fracture			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 trauma activated			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Patella fracture			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
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			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural pain			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative haematoma			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Postoperative hypotension			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Rib fracture			

subjects affected / exposed	2 / 483 (0.41%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scapula fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Spinal compression fracture			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Subarachnoid bleeding			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma (traumatic)			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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 T12			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Traffic accident			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Trochanteric femoral fracture			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
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 fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Wound dehiscence			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Bronchogenic cyst			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 myocardial infarction			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	2 / 484 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina pectoris aggravated			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Angina unstable			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Aortic valve stenosis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Arrhythmia			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	2 / 484 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation aggravated			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation with rapid ventricular response			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 flutter			

subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Bradycardia			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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 disease			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Coronary artery disease aggravated			
subjects affected / exposed	2 / 483 (0.41%)	0 / 484 (0.00%)	0 / 484 (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
Myocardial infarction			
subjects affected / exposed	0 / 483 (0.00%)	2 / 484 (0.41%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non ST segment elevation myocardial infarction			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Paroxysmal supraventricular tachycardia			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Recurrent atrial fibrillation			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Sick sinus syndrome			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Sinus bradycardia			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular bigeminy			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right coronary artery stenosis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	0 / 484 (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
Cerebrovascular accident			

subjects affected / exposed	0 / 483 (0.00%)	2 / 484 (0.41%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complex partial seizures			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia aggravated			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epileptic seizure			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Felt faint			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lightheadedness			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurocardiogenic syncope			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Nonconvulsive status epilepticus			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Seizure			
subjects affected / exposed	2 / 483 (0.41%)	1 / 484 (0.21%)	0 / 484 (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
Stroke			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Syncopal attack			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Syncope			
subjects affected / exposed	5 / 483 (1.04%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamic infarction			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 cerebral ischaemia			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient global amnesia			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 483 (0.00%)	3 / 484 (0.62%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor aggravated			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Unconsciousness			

subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Dysarthria			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurologic reaction			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Benign paroxysmal positional vertigo			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cataract bilateral NOS			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right cataract			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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 disorders			
Abdominal pain			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	0 / 484 (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
Acute enterocolitis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Diarrhoea			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Diverticular perforation			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Duodenal ulcer			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Gastric ulcer			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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 obstruction			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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 upset			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Haematochezia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Haemorrhoids aggravated			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Indirect inguinal hernia			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 483 (0.41%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	2 / 483 (0.41%)	0 / 484 (0.00%)	0 / 484 (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
Left inguinal hernia			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left upper quadrant pain			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Oesophageal ulcer			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reflux oesophagitis			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Right inguinal hernia			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenderness epigastric			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 483 (0.00%)	2 / 484 (0.41%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular disease			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyloric ulcer perforation			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	2 / 483 (0.41%)	0 / 484 (0.00%)	0 / 484 (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
Biliary tract disorder			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	2 / 484 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	0 / 484 (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
Skin and subcutaneous tissue disorders			
Exanthem			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Urticarial rash			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Hives			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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 renal			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Calculus ureteric			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Haematuria			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Hydronephrosis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Kidney stone			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Renal failure acute			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	0 / 484 (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
Renal mass			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stone urinary bladder			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Stress urinary incontinence			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteral stricture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Ureterolithiasis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Urolithiasis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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

Cervical spinal stenosis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spondylosis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Coxarthrosis			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	0 / 484 (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
Herniated disc			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herniated nucleus pulposus			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Hips osteoarthritis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Knee osteoarthritis			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	0 / 484 (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
Lumbar disc herniation			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Musculoskeletal chest pain			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Myalgia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Osteoarthritis aggravated			
subjects affected / exposed	3 / 483 (0.62%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff tear			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Spinal stenosis NOS			

subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Back muscle spasms			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute appendicitis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
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 diverticulitis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Bacillus bacteraemia			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial parotitis			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Bacterial sepsis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 of foot			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis of hand			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 of leg			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	0 / 484 (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
Diverticulitis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Influenza B virus infection			
subjects affected / exposed	0 / 483 (0.00%)	2 / 484 (0.41%)	0 / 484 (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
Liver abscess			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Lobar pneumonia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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 infection			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
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			
subjects affected / exposed	2 / 483 (0.41%)	2 / 484 (0.41%)	3 / 484 (0.62%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia bacterial			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prosthesis related infection			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Pseudomonas infection			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Pyelonephritis			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Septic arthritis			

subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Septic shock			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
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 cord infection			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 483 (0.62%)	1 / 484 (0.21%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 483 (0.00%)	1 / 484 (0.21%)	0 / 484 (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
Viral syndrome			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	1 / 484 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial prostatitis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza A virus infection			

subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 483 (0.41%)	1 / 484 (0.21%)	0 / 484 (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			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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			
subjects affected / exposed	1 / 483 (0.21%)	1 / 484 (0.21%)	0 / 484 (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
Hyponatraemia aggravated			
subjects affected / exposed	1 / 483 (0.21%)	0 / 484 (0.00%)	0 / 484 (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
Hypercalcaemia			
subjects affected / exposed	0 / 483 (0.00%)	0 / 484 (0.00%)	0 / 484 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm A. Verubecestat 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 2)	Arm C. Verubecestat 40 mg (Part 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 197 (5.08%)	22 / 191 (11.52%)	24 / 204 (11.76%)
number of deaths (all causes)	0	3	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of prostate			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical fibroxanthoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	4 / 197 (2.03%)	2 / 191 (1.05%)	3 / 204 (1.47%)
occurrences causally related to treatment / all	0 / 4	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Breast cancer metastatic			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer recurrent			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carcinoma in situ of breast ductal			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic tubular adenoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Follicular thyroid cancer			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric adenoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lentigo melanoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip basal cell carcinoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma metastatic			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melanoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melanoma in situ			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic gastric cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple myeloma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodular basal cell carcinoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreas cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
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 recurrent			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate carcinoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin carcinoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 197 (0.51%)	0 / 191 (0.00%)	0 / 204 (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 of head and neck			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 197 (0.51%)	0 / 191 (0.00%)	0 / 204 (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 of skin in situ			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin well differentiated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the nasal cavity			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial basal cell carcinoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Throat cancer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urothelial carcinoma			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
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			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial stenosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive episode			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral obliterative arteriopathy			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			

subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
General disorders and administration site conditions			
Acute chest pain			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain aggravated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pressure			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever of unknown origin			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait abnormal			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity reaction			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Bartholin's cyst			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hypertrophy			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystocele			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urogenital prolapse			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease exacerbation			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Collapse of lung			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal haematoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Pneumothorax			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute mania			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusion aggravated			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychosis aggravated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic episode			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somatisation disorder			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unsuccessful suicide			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute delirium			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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			
Creatinine increased			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecal occult blood			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic specific antigen increased			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol intoxication			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arm fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bimalleolar fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bruise of head			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic subdural haematoma			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Finger injury			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture of intertrochanteric section of femur, closed			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured mandible			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint ligament rupture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spine compression fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Near drowning			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Olecranon fracture			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain trauma activated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural pain			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative haematoma			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative hypotension			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			

subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Scapula fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid bleeding			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma (traumatic)			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture T12			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traffic accident			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trochanteric femoral fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral fracture			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Wound dehiscence			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Traumatic fracture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
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			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Bronchogenic cyst			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris aggravated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Aortic valve stenosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation aggravated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation with rapid ventricular response			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease aggravated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
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			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Non ST segment elevation myocardial infarction			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paroxysmal supraventricular tachycardia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Recurrent atrial fibrillation			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular bigeminy			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Right coronary artery stenosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complex partial seizures			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia aggravated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 197 (0.51%)	0 / 191 (0.00%)	0 / 204 (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
Embolic stroke			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epileptic seizure			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Felt faint			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lightheadedness			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurocardiogenic syncope			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nonconvulsive status epilepticus			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 197 (0.51%)	1 / 191 (0.52%)	0 / 204 (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
Stroke			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncopal attack			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Thalamic infarction			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient cerebral ischaemia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient global amnesia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor aggravated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unconsciousness			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurologic reaction			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Benign paroxysmal positional vertigo			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cataract bilateral NOS			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right cataract			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute enterocolitis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal upset			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids aggravated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Indirect inguinal hernia			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left inguinal hernia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left upper quadrant pain			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal ulcer			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal prolapse			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reflux oesophagitis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right inguinal hernia			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenderness epigastric			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular disease			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Pyloric ulcer perforation			

subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract disorder			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Exanthem			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticarial rash			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hives			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus renal			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney stone			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal mass			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stone urinary bladder			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress urinary incontinence			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteral stricture			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urolithiasis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cervical spinal stenosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spondylosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coxarthrosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herniated disc			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herniated nucleus pulposus			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hips osteoarthritis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee osteoarthritis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar disc herniation			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis aggravated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff tear			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis NOS			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back muscle spasms			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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			
Acute appendicitis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute diverticulitis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacillus bacteraemia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial parotitis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis of foot			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis of hand			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis of leg			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza B virus infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 191 (0.00%)	0 / 204 (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 bacterial			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prosthesis related infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic arthritis			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral syndrome			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial prostatitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 191 (0.00%)	0 / 204 (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
Gastroenteritis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza A virus infection			

subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia aggravated			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 191 (0.52%)	0 / 204 (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

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

Non-serious adverse events	Arm A. Verubecestat 12 mg (Part 1)	Arm B. Verubecestat 40 mg (Part 1)	Arm C. Placebo (Part 1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	221 / 483 (45.76%)	223 / 484 (46.07%)	202 / 484 (41.74%)
Investigations			
Weight decreased			
subjects affected / exposed	27 / 483 (5.59%)	32 / 484 (6.61%)	10 / 484 (2.07%)
occurrences (all)	27	32	10
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	42 / 483 (8.70%)	36 / 484 (7.44%)	33 / 484 (6.82%)
occurrences (all)	56	48	41
Nervous system disorders			
Dizziness			
subjects affected / exposed	37 / 483 (7.66%)	31 / 484 (6.40%)	25 / 484 (5.17%)
occurrences (all)	49	36	25
Headache			
subjects affected / exposed	32 / 483 (6.63%)	26 / 484 (5.37%)	24 / 484 (4.96%)
occurrences (all)	36	27	28
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	28 / 483 (5.80%)	21 / 484 (4.34%)	36 / 484 (7.44%)
occurrences (all)	35	22	38
Psychiatric disorders			
Depression			
subjects affected / exposed	17 / 483 (3.52%)	28 / 484 (5.79%)	13 / 484 (2.69%)
occurrences (all)	17	29	15
Suicidal ideation			
subjects affected / exposed	31 / 483 (6.42%)	40 / 484 (8.26%)	25 / 484 (5.17%)
occurrences (all)	48	50	26
Infections and infestations			
Cold			
subjects affected / exposed	16 / 483 (3.31%)	25 / 484 (5.17%)	24 / 484 (4.96%)
occurrences (all)	20	28	34
Common cold syndrome			
subjects affected / exposed	22 / 483 (4.55%)	32 / 484 (6.61%)	26 / 484 (5.37%)
occurrences (all)	33	48	38
Upper respiratory tract infection			

subjects affected / exposed	31 / 483 (6.42%)	21 / 484 (4.34%)	31 / 484 (6.40%)
occurrences (all)	37	24	38
Urinary tract infection			
subjects affected / exposed	30 / 483 (6.21%)	26 / 484 (5.37%)	23 / 484 (4.75%)
occurrences (all)	37	35	30

Non-serious adverse events	Arm A. Verubecestat 12 mg (Part 2)	Arm B. Verubecestat 40 mg (Part 2)	Arm C. Verubecestat 40 mg (Part 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 197 (19.80%)	31 / 191 (16.23%)	40 / 204 (19.61%)
Investigations			
Weight decreased			
subjects affected / exposed	6 / 197 (3.05%)	0 / 191 (0.00%)	8 / 204 (3.92%)
occurrences (all)	6	0	8
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	8 / 197 (4.06%)	6 / 191 (3.14%)	7 / 204 (3.43%)
occurrences (all)	8	8	10
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 197 (2.03%)	6 / 191 (3.14%)	4 / 204 (1.96%)
occurrences (all)	4	6	4
Headache			
subjects affected / exposed	0 / 197 (0.00%)	0 / 191 (0.00%)	0 / 204 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 197 (3.05%)	2 / 191 (1.05%)	3 / 204 (1.47%)
occurrences (all)	7	2	3
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 197 (1.52%)	0 / 191 (0.00%)	2 / 204 (0.98%)
occurrences (all)	3	0	2
Suicidal ideation			
subjects affected / exposed	6 / 197 (3.05%)	5 / 191 (2.62%)	5 / 204 (2.45%)
occurrences (all)	6	5	5
Infections and infestations			

Cold			
subjects affected / exposed	1 / 197 (0.51%)	4 / 191 (2.09%)	3 / 204 (1.47%)
occurrences (all)	1	4	3
Common cold syndrome			
subjects affected / exposed	9 / 197 (4.57%)	3 / 191 (1.57%)	3 / 204 (1.47%)
occurrences (all)	10	3	3
Upper respiratory tract infection			
subjects affected / exposed	3 / 197 (1.52%)	6 / 191 (3.14%)	4 / 204 (1.96%)
occurrences (all)	4	6	4
Urinary tract infection			
subjects affected / exposed	3 / 197 (1.52%)	3 / 191 (1.57%)	8 / 204 (3.92%)
occurrences (all)	3	4	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2014	Amendment 05: Primary reasons for amendment were to: 1) include routine skin monitoring; 2) update details related to the Screening PET scan; 3) update details related to monitoring by magnetic resonance imaging (MRI); and 4) discontinue iris monitoring and procedures assessing intraocular pressure.
15 June 2015	Amendment 06: Primary reasons for amendment were to: 1) discontinue ophthalmologic monitoring; 2) revise discontinuation criteria; and 3) revise events of clinical interest.
07 August 2015	Amendment 07: Primary reason for amendment was to add a long-term safety and efficacy extension to the initial 104-week trial.
02 March 2017	Amendment 11: Primary reasons for amendment were to: 1) reinstate collection of plasma pharmacokinetic (PK) samples; 2) clarify unblinding protocol; 3) make optional the conduct of the futility interim analysis; 4) reduce sample size; and 5) add an exploratory tau PET imaging sub study.
02 March 2017	Amendment 12: Primary reasons for amendment were to: 1) clarify unblinding protocol; and 2) update projected enrollment. This amendment applied specifically to the long-term extension.
12 January 2018	Amendment 15: Primary reason for amendment was to update eligibility criteria for the long-term extension.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 February 2018	Study terminated early.	-

Notes:

Limitations and caveats

None reported