

**Clinical trial results:****A Randomized, Open-Label, Phase 3 Study of Abemaciclib Combined with Standard Adjuvant Endocrine Therapy versus Standard Adjuvant Endocrine Therapy Alone in Patients with High Risk, Node Positive, Early Stage, Hormone Receptor Positive, Human Epidermal Receptor 2 Negative, Breast Cancer****Summary**

EudraCT number	2016-004362-26
Trial protocol	DE NL HU GB BE DK FI PL GR AT ES CZ FR PT IT RO
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	31 March 2021
First version publication date	31 March 2021

Trial information**Trial identification**

Sponsor protocol code	I3Y-MC-JPCF
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03155997
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16338

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	Interim
Date of interim/final analysis	16 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of the study drug abemaciclib in participants with high risk, node positive, early stage, hormone receptor positive (HR+), human epidermal receptor 2 negative (HER2-), breast cancer.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 July 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 145
Country: Number of subjects enrolled	Australia: 217
Country: Number of subjects enrolled	Austria: 42
Country: Number of subjects enrolled	Belgium: 116
Country: Number of subjects enrolled	Brazil: 297
Country: Number of subjects enrolled	Canada: 44
Country: Number of subjects enrolled	China: 357
Country: Number of subjects enrolled	Czechia: 27
Country: Number of subjects enrolled	Denmark: 112
Country: Number of subjects enrolled	Finland: 94
Country: Number of subjects enrolled	France: 187
Country: Number of subjects enrolled	Germany: 300
Country: Number of subjects enrolled	Greece: 138
Country: Number of subjects enrolled	Hong Kong: 20
Country: Number of subjects enrolled	Hungary: 52
Country: Number of subjects enrolled	India: 112
Country: Number of subjects enrolled	Israel: 77
Country: Number of subjects enrolled	Italy: 131
Country: Number of subjects enrolled	Japan: 377
Country: Number of subjects enrolled	Mexico: 225
Country: Number of subjects enrolled	Netherlands: 19

Country: Number of subjects enrolled	New Zealand: 43
Country: Number of subjects enrolled	Poland: 125
Country: Number of subjects enrolled	Portugal: 37
Country: Number of subjects enrolled	Puerto Rico: 4
Country: Number of subjects enrolled	Romania: 113
Country: Number of subjects enrolled	Russian Federation: 139
Country: Number of subjects enrolled	Saudi Arabia: 14
Country: Number of subjects enrolled	Singapore: 32
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	Korea, Republic of: 245
Country: Number of subjects enrolled	Spain: 292
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	Taiwan: 124
Country: Number of subjects enrolled	Turkey: 235
Country: Number of subjects enrolled	Ukraine: 105
Country: Number of subjects enrolled	United Kingdom: 199
Country: Number of subjects enrolled	United States: 820
Worldwide total number of subjects	5637
EEA total number of subjects	1797

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)	4787
From 65 to 84 years	850
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Completers included participants who had recurrence disease, death due to any cause, and participants off treatment but on study follow-up.

Pre-assignment

Screening details:

No Text Available

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	150 mg Abemaciclib + Endocrine Therapy

Arm description:

Participants received Abemaciclib orally at 150 milligrams (mg) twice daily with at least 6 hours between doses for up to 2 years or until evidence of disease recurrence or other discontinuation criteria were met, whichever occurs first. Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	LY2835219
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Abemaciclib orally at 150 milligrams (mg) twice daily with at least 6 hours between doses for up to 2 years or until evidence of disease recurrence or other discontinuation criteria were met, whichever occurs first.

Investigational medicinal product name	Standard Adjuvant Endocrine Therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Oral liquid, Tablet
Routes of administration	Intramuscular use, Oral use, Subcutaneous use

Dosage and administration details:

Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

Arm title	Endocrine Therapy
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Arm description:

Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

Arm type	Active comparator
Investigational medicinal product name	Standard Adjuvant Endocrine Therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Oral liquid, Tablet
Routes of administration	Intramuscular use, Oral use, Subcutaneous use

Dosage and administration details:

Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

Number of subjects in period 1	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy
Started	2808	2829
Received at least one dose of study drug	2791	2800
Completed	650	607
Not completed	2158	2222
Missing disposition data	-	1
Consent withdrawn by subject	119	134
On study treatment	2027	2074
Lost to follow-up	12	13

Baseline characteristics

Reporting groups

Reporting group title	150 mg Abemaciclib + Endocrine Therapy
Reporting group description:	
Participants received Abemaciclib orally at 150 milligrams (mg) twice daily with at least 6 hours between doses for up to 2 years or until evidence of disease recurrence or other discontinuation criteria were met, whichever occurs first. Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.	
Reporting group title	Endocrine Therapy
Reporting group description:	
Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.	

Reporting group values	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy	Total
Number of subjects	2808	2829	5637
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	52.20	52.10	
standard deviation	± 11.26	± 11.20	-
Gender categorical			
Units: Subjects			
Female	2787	2814	5601
Male	21	15	36
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	355	378	733
Not Hispanic or Latino	1734	1738	3472
Unknown or Not Reported	719	713	1432
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	64	58	122
Asian	675	669	1344
Native Hawaiian or Other Pacific Islander	3	4	7
Black or African American	57	53	110
White	1947	1978	3925
More than one race	22	25	47

Unknown or Not Reported	40	42	82
Region of Enrollment			
Units: Subjects			
Argentina	77	68	145
Australia	108	109	217
Austria	22	20	42
Belgium	65	51	116
Brazil	144	153	297
Canada	28	16	44
China	187	170	357
Czechia	15	12	27
Denmark	54	58	112
Finland	45	49	94
France	86	101	187
Germany	148	152	300
Greece	74	64	138
Hong Kong	8	12	20
Hungary	24	28	52
India	59	53	112
Israel	39	38	77
Italy	72	59	131
Japan	181	196	377
Mexico	104	121	225
Netherlands	5	14	19
New Zealand	21	22	43
Poland	65	60	125
Portugal	21	16	37
Puerto Rico	1	3	4
Romania	53	60	113
Russia	66	73	139
Saudi Arabia	5	9	14
Singapore	11	21	32
South Africa	3	6	9
South Korea	122	123	245
Spain	144	148	292
Sweden	7	5	12
Taiwan	64	60	124
Turkey	125	110	235
Ukraine	54	51	105
United Kingdom	99	100	199
United States	402	418	820

End points

End points reporting groups

Reporting group title	150 mg Abemaciclib + Endocrine Therapy
Reporting group description: Participants received Abemaciclib orally at 150 milligrams (mg) twice daily with at least 6 hours between doses for up to 2 years or until evidence of disease recurrence or other discontinuation criteria were met, whichever occurs first. Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.	
Reporting group title	Endocrine Therapy
Reporting group description: Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.	

Primary: Invasive Disease Free Survival (IDFS)

End point title	Invasive Disease Free Survival (IDFS)
End point description: IDFS, as defined by the STEEP System, was measured from the date of randomization to the date of first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary non-breast invasive cancer, death attributable to any cause. Analysis Population Description: All randomized participants (including the censored participants). 2672 participants were censored in "150 mg Abemaciclib + Endocrine Therapy," 2642 participants were censored in "Endocrine Therapy."	
End point type	Primary
End point timeframe: Baseline to Recurrence or Death from Any Cause (Up to 32 Months)	

End point values	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2808 ^[1]	2829 ^[2]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[1] - 9999 = NA, There were not enough events to compute a median or 95% confidence interval.

[2] - 9999 = NA, There were not enough events to compute a median or 95% confidence interval.

Statistical analyses

Statistical analysis title	Invasive Disease Free Survival (IDFS)
Comparison groups	150 mg Abemaciclib + Endocrine Therapy v Endocrine Therapy

Number of subjects included in analysis	5637
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00957
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.747
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.598
upper limit	0.932

Secondary: IDFS for Participants with Ki-67 Index $\geq 20\%$

End point title	IDFS for Participants with Ki-67 Index $\geq 20\%$
End point description:	
Outcome data will be provided after the study is completed.	
End point type	Secondary
End point timeframe:	
Baseline to Recurrence or Death from Any Cause (Approximately 10 Years)	

End point values	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[3] - Outcome data will be provided after the study is completed.

[4] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Relapse-Free Survival (DRFS)

End point title	Distant Relapse-Free Survival (DRFS)
End point description:	
Distant relapse-free survival is defined as the time from randomization to distant recurrence or death from any cause, whichever occurs first.	
Analysis Population Description: All randomized participants (including the censored participants). 2702 participants were censored in "150 mg Abemaciclib + Endocrine Therapy," 2677 participants were censored in "Endocrine Therapy."	
End point type	Secondary
End point timeframe:	
Baseline to Distant Recurrence or Death from Any Cause (Up to 32 Months)	

End point values	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2808 ^[5]	2829 ^[6]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[5] - 9999 = NA, There were not enough events to compute a median or 95% confidence interval.

[6] - 9999 = NA, There were not enough events to compute a median or 95% confidence interval.

Statistical analyses

Statistical analysis title	Distant Relapse-Free Survival (DRFS)
Comparison groups	150 mg Abemaciclib + Endocrine Therapy v Endocrine Therapy
Number of subjects included in analysis	5637
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.717
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.559
upper limit	0.92

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Outcome data will be provided after the study is completed.	
End point type	Secondary
End point timeframe:	
Baseline to Death from Any Cause (Approximately 10 Years)	

End point values	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[7]	0 ^[8]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[7] - Outcome data will be provided after the study is completed.

[8] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Minimum Steady State Concentration (C_{min,ss}) of Abemaciclib

End point title	Pharmacokinetics (PK): Minimum Steady State Concentration (C _{min,ss}) of Abemaciclib ^[9]
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End point description:

Pharmacokinetics (PK): Minimum Steady State Concentration (C_{min,ss}) of Abemaciclib

Analysis Population Description: All randomized participants who received at least one dose of Abemaciclib and had evaluable PK data.

End point type	Secondary
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End point timeframe:

Day 1 (2 hours post-dose), Days 30, 60, 90 post-dose

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No inferential statistics were planned for this endpoint.

End point values	150 mg Abemaciclib + Endocrine Therapy			
Subject group type	Reporting group			
Number of subjects analysed	483			
Units: Nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	143 (± 110)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline on the Functional Assessment of Cancer Therapy - Breast (FACT-B)

End point title	Change from Baseline on the Functional Assessment of Cancer Therapy - Breast (FACT-B)
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End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary
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End point timeframe:

Baseline, Follow Up (Approximately 3 Years)

End point values	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[10]	0 ^[11]		
Units: Score on a scale				
least squares mean (standard error)	()	()		

Notes:

[10] - Outcome data will be provided after the study is completed.

[11] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline on the Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES)

End point title	Change from Baseline on the Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES)
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End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary
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End point timeframe:

Baseline, Follow Up (Approximately 3 Years)]

End point values	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[12]	0 ^[13]		
Units: Score on a scale				
least squares mean (standard error)	()	()		

Notes:

[12] - Outcome data will be provided after the study is completed.

[13] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline on the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F)

End point title	Change from Baseline on the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F)
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End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary
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End point timeframe:

Baseline, Follow Up (Approximately 3 Years)]

End point values	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[14]	0 ^[15]		
Units: Score on a scale				
least squares mean (standard error)	()	()		

Notes:

[14] - Outcome data will be provided after the study is completed.

[15] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline on the EuroQol Five-Dimension Five-Level Questionnaire (EQ-5D-5L)

End point title	Change from Baseline on the EuroQol Five-Dimension Five-Level Questionnaire (EQ-5D-5L)
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End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary
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End point timeframe:

Baseline, Follow Up (Approximately 3 Years)]

End point values	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[16]	0 ^[17]		
Units: Score on a scale				
least squares mean (standard error)	()	()		

Notes:

[16] - Outcome data will be provided after the study is completed.

[17] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline Up To 32 Months

Adverse event reporting additional description:

I3Y-MC-JPCF

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	150 mg Abemaciclib + Endocrine Therapy
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Reporting group description:

Participants received Abemaciclib orally at 150 milligrams (mg) twice daily with at least 6 hours between doses for up to 2 years or until evidence of disease recurrence or other discontinuation criteria were met, whichever occurs first. Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

Reporting group title	Endocrine Therapy
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Reporting group description:

Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

Serious adverse events	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	344 / 2791 (12.33%)	202 / 2800 (7.21%)	
number of deaths (all causes)	38	36	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
acute lymphocytic leukaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cervix carcinoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed ^[1]	0 / 2770 (0.00%)	2 / 2785 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
colon cancer			

alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colorectal carcinoma stage 0			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
endometrial neoplasm			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed ^[2]	0 / 2770 (0.00%)	1 / 2785 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
fibroadenoma of breast			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal adenocarcinoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
malignant melanoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
meningioma benign			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
non-small cell lung cancer			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
papillary thyroid cancer			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
thyroid adenoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
thyroid cancer			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
uterine leiomyoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed ^[3]	1 / 2770 (0.04%)	2 / 2785 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	16 / 2791 (0.57%)	3 / 2800 (0.11%)	
occurrences causally related to treatment / all	12 / 17	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
embolism			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemorrhage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
jugular vein thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lymphoedema			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	5 / 2791 (0.18%)	3 / 2800 (0.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral artery thrombosis alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombophlebitis alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombophlebitis superficial alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
capsular contracture associated with breast implant alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
chest pain alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 2791 (0.14%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
fatigue alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 2791 (0.14%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
hyperplasia alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
impaired healing alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	3 / 2800 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
inflammation alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
non-cardiac chest pain alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

pyrexia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	7 / 2791 (0.25%) 4 / 7 0 / 0	0 / 2800 (0.00%) 0 / 0 0 / 0	
sudden death alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 2791 (0.00%) 0 / 0 0 / 0	1 / 2800 (0.04%) 0 / 1 0 / 0	
Immune system disorders anaphylactic reaction alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2791 (0.04%) 0 / 1 0 / 0	1 / 2800 (0.04%) 0 / 1 0 / 0	
drug hypersensitivity alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2791 (0.04%) 0 / 1 0 / 0	0 / 2800 (0.00%) 0 / 0 0 / 0	
Reproductive system and breast disorders adenomyosis alternative dictionary used: MedDRA 23.0 subjects affected / exposed ^[4] occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2770 (0.04%) 1 / 1 0 / 0	0 / 2785 (0.00%) 0 / 0 0 / 0	
breast atrophy alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 2791 (0.00%) 0 / 0 0 / 0	1 / 2800 (0.04%) 0 / 2 0 / 0	
breast calcifications			

alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast discharge			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast fibrosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast inflammation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast mass			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast necrosis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast swelling			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cervical dysplasia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed ^[5]	2 / 2770 (0.07%)	0 / 2785 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
endometrial disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed ^[6]	0 / 2770 (0.00%)	1 / 2785 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
endometrial hypertrophy			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed ^[7]	0 / 2770 (0.00%)	2 / 2785 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
endometrial thickening			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed ^[8]	1 / 2770 (0.04%)	1 / 2785 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

<p>endometriosis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[9]</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>0 / 2770 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 2785 (0.04%)</p> <p>1 / 1</p> <p>0 / 0</p>	
<p>fibrocystic breast disease</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>0 / 2791 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>2 / 2800 (0.07%)</p> <p>0 / 2</p> <p>0 / 0</p>	
<p>metrorrhagia</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[10]</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>0 / 2770 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 2785 (0.04%)</p> <p>0 / 1</p> <p>0 / 0</p>	
<p>ovarian cyst</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[11]</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>0 / 2770 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>3 / 2785 (0.11%)</p> <p>0 / 3</p> <p>0 / 0</p>	
<p>pelvic haematoma</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 2791 (0.04%)</p> <p>0 / 1</p> <p>0 / 0</p>	<p>0 / 2800 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	
<p>uterine polyp</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[12]</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>2 / 2770 (0.07%)</p> <p>0 / 2</p> <p>0 / 0</p>	<p>3 / 2785 (0.11%)</p> <p>1 / 3</p> <p>0 / 0</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>asthma</p> <p>alternative dictionary used: MedDRA 23.0</p>			

subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspnoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoxia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
interstitial lung disease			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
organising pneumonia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	2 / 2791 (0.07%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia aspiration			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	7 / 2791 (0.25%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	6 / 7	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	16 / 2791 (0.57%)	3 / 2800 (0.11%)	
occurrences causally related to treatment / all	14 / 16	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
respiratory failure			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
bipolar disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
confusional state			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
delirium			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
depression			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
mania			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
mental disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
psychotic disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
suicide attempt			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Product issues			
device failure			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 2791 (0.18%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 2791 (0.18%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood creatinine increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
international normalised ratio increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
occult blood			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
transaminases increased			

alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
abdominal wound dehiscence			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
alcohol poisoning			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ankle fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	3 / 2800 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast procedural complication			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
clavicle fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
exposure during pregnancy			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fall			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
femoral neck fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
foot fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hip fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
humerus fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

incisional hernia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
jaw fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
joint injury			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ligament rupture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
post procedural haematoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
post procedural haemorrhage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
postoperative adhesion			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
postoperative thoracic procedure complication			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
postoperative wound complication			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
procedural complication			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
radiation pneumonitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 2791 (0.11%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
radius fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rib fracture			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	2 / 2791 (0.07%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin flap necrosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
thermal burn			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound complication			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound dehiscence			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	4 / 2800 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound necrosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

wrist fracture alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2791 (0.04%) 0 / 1 0 / 0	1 / 2800 (0.04%) 0 / 1 0 / 0	
Cardiac disorders acute left ventricular failure alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2791 (0.04%) 0 / 1 0 / 0	0 / 2800 (0.00%) 0 / 0 0 / 0	
angina pectoris alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2791 (0.04%) 1 / 1 0 / 0	0 / 2800 (0.00%) 0 / 0 0 / 0	
atrial fibrillation alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	6 / 2791 (0.21%) 2 / 6 0 / 0	1 / 2800 (0.04%) 0 / 1 0 / 0	
atrioventricular block complete alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 2791 (0.00%) 0 / 0 0 / 0	1 / 2800 (0.04%) 0 / 1 0 / 0	
cardiac arrest alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 2791 (0.07%) 1 / 2 0 / 1	0 / 2800 (0.00%) 0 / 0 0 / 0	
cardiac failure alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	4 / 2791 (0.14%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
cardiotoxicity			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
coronary artery disease			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 2791 (0.14%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
myocardial ischaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pericarditis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
sinus tachycardia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

stress cardiomyopathy alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
supraventricular tachycardia alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ventricular fibrillation alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
carotid artery aneurysm alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
carpal tunnel syndrome alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral haemorrhage alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
cerebral infarction alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral ischaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral venous thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebrospinal fluid leakage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebrovascular accident			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
dizziness			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
extrapyramidal disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

headache			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hemiparesis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ischaemic stroke			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 2791 (0.11%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
memory impairment			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
monoparesis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
movement disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
nerve compression			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neuropathy			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
presyncope			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
subarachnoid haemorrhage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 2791 (0.14%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
transient ischaemic attack			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
trigeminal neuralgia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	8 / 2791 (0.29%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	4 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
bone marrow oedema			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
disseminated intravascular coagulation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 2791 (0.14%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
leukopenia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 2791 (0.14%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lymphadenopathy mediastinal			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	3 / 2791 (0.11%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancytopenia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombocytopenia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 2791 (0.14%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
tympanic membrane perforation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vertigo			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
angle closure glaucoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cataract			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
eyelid ptosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
macular hole			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
macular pseudohole			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
retinal detachment			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	6 / 2791 (0.21%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal fissure			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal fistula			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
chronic gastritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 2791 (0.11%)	3 / 2800 (0.11%)	
occurrences causally related to treatment / all	2 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis ischaemic			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dental caries			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	15 / 2791 (0.54%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	13 / 18	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

enteritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
food poisoning			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastritis erosive			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal fistula			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemorrhoidal haemorrhage			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemorrhoids			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
inguinal hernia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal obstruction			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 2791 (0.11%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
large intestine polyp			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 2791 (0.11%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophagitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

pancreatitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	6 / 2791 (0.21%) 1 / 6 0 / 0	2 / 2800 (0.07%) 0 / 2 0 / 0	
pancreatitis acute alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 2791 (0.07%) 1 / 2 0 / 0	0 / 2800 (0.00%) 0 / 0 0 / 0	
peritoneal adhesions alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 2791 (0.00%) 0 / 0 0 / 0	1 / 2800 (0.04%) 0 / 1 0 / 0	
stomatitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 2791 (0.07%) 1 / 2 0 / 0	0 / 2800 (0.00%) 0 / 0 0 / 0	
umbilical hernia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 2791 (0.00%) 0 / 0 0 / 0	1 / 2800 (0.04%) 0 / 1 0 / 0	
vomiting alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 2791 (0.11%) 2 / 3 0 / 0	0 / 2800 (0.00%) 0 / 0 0 / 0	
Hepatobiliary disorders biliary colic alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholecystitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	10 / 2791 (0.36%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	1 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholecystitis acute			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholelithiasis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	3 / 2800 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
drug-induced liver injury			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic cirrhosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic function abnormal			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

jaundice alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 2791 (0.00%) 0 / 0 0 / 0	 1 / 2800 (0.04%) 0 / 1 0 / 0	
Skin and subcutaneous tissue disorders erythema alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 2791 (0.00%) 0 / 0 0 / 0	 1 / 2800 (0.04%) 0 / 1 0 / 0	
Renal and urinary disorders acute kidney injury alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 4 / 2791 (0.14%) 3 / 4 0 / 0	 0 / 2800 (0.00%) 0 / 0 0 / 0	
nephrolithiasis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 3 / 2791 (0.11%) 0 / 3 0 / 0	 1 / 2800 (0.04%) 0 / 1 0 / 0	
renal failure alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 2 / 2791 (0.07%) 1 / 2 0 / 0	 0 / 2800 (0.00%) 0 / 0 0 / 0	
renal impairment alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 2791 (0.04%) 1 / 1 0 / 0	 0 / 2800 (0.00%) 0 / 0 0 / 0	
tubulointerstitial nephritis alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fistula			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
flank pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intervertebral disc protrusion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	3 / 2800 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
myositis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neck pain			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteoarthritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteonecrosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rheumatoid arthritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rotator cuff syndrome			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal osteoarthritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
tenosynovitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations abdominal infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 2791 (0.00%) 0 / 0 0 / 0	1 / 2800 (0.04%) 0 / 1 0 / 0	
abscess alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2791 (0.04%) 1 / 1 0 / 0	0 / 2800 (0.00%) 0 / 0 0 / 0	
anal abscess alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2791 (0.04%) 0 / 1 0 / 0	0 / 2800 (0.00%) 0 / 0 0 / 0	
appendicitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 2791 (0.11%) 0 / 3 0 / 0	2 / 2800 (0.07%) 0 / 2 0 / 0	
appendicitis perforated alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2791 (0.04%) 0 / 1 0 / 0	0 / 2800 (0.00%) 0 / 0 0 / 0	
bacteraemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 2791 (0.07%) 1 / 2 0 / 0	1 / 2800 (0.04%) 0 / 1 0 / 0	
biliary tract infection alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast abscess			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 2791 (0.11%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast cellulitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 2791 (0.18%)	4 / 2800 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
campylobacter gastroenteritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cellulitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	11 / 2791 (0.39%)	9 / 2800 (0.32%)	
occurrences causally related to treatment / all	1 / 13	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
cellulitis staphylococcal			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

clostridium colitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
clostridium difficile colitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
coronavirus infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
device related infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
diverticulitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 2791 (0.11%)	5 / 2800 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
ear infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
erysipelas			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	5 / 2791 (0.18%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	3 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
escherichia pyelonephritis alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile infection alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis clostridial alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatitis e alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
implant site infection alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
infective pulmonary exacerbation of cystic fibrosis alternative dictionary used: MedDRA 23.0 subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
influenza alternative dictionary used: MedDRA 23.0 subjects affected / exposed	7 / 2791 (0.25%)	3 / 2800 (0.11%)		
occurrences causally related to treatment / all	1 / 7	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 1		
intervertebral discitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
laryngitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
lower respiratory tract infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
lymphangitis alternative dictionary used: MedDRA 23.0				

subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mastitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 2791 (0.11%)	5 / 2800 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
mastoiditis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
meningitis viral			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
nasopharyngitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenic infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteomyelitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

peritonitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	23 / 2791 (0.82%)	14 / 2800 (0.50%)	
occurrences causally related to treatment / all	10 / 23	2 / 15	
deaths causally related to treatment / all	0 / 0	0 / 1	
pneumonia bacterial			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia influenzal			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia streptococcal			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
post procedural cellulitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
post procedural infection			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
postoperative wound infection alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyelonephritis alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory tract infection alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 2791 (0.18%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
septic shock alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
skin infection alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

soft tissue infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tuberculosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper respiratory tract infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	6 / 2791 (0.21%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	12 / 2791 (0.43%)	4 / 2800 (0.14%)	
occurrences causally related to treatment / all	1 / 12	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
urosepsis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
viral infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound infection			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	2 / 2791 (0.07%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
dehydration			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	7 / 2791 (0.25%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	5 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
food intolerance			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypercalcaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperglycaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypocalcaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	4 / 2791 (0.14%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyponatraemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	2 / 2800 (0.07%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypophosphataemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypovolaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 2791 (0.00%)	1 / 2800 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
metabolic acidosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 2791 (0.04%)	0 / 2800 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	150 mg Abemaciclib + Endocrine Therapy	Endocrine Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2723 / 2791 (97.56%)	2318 / 2800 (82.79%)	
Vascular disorders			
hot flush			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	393 / 2791 (14.08%)	587 / 2800 (20.96%)	
occurrences (all)	432	678	
hypertension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	101 / 2791 (3.62%)	130 / 2800 (4.64%)	
occurrences (all)	120	158	
hypotension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	33 / 2791 (1.18%)	14 / 2800 (0.50%)	
occurrences (all)	33	15	
lymphoedema			

alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	282 / 2791 (10.10%) 295	207 / 2800 (7.39%) 225	
Surgical and medical procedures breast reconstruction alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	28 / 2791 (1.00%) 28	22 / 2800 (0.79%) 25	
General disorders and administration site conditions axillary pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) chest pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) chills alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) fatigue alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	28 / 2791 (1.00%) 28 35 / 2791 (1.25%) 40 49 / 2791 (1.76%) 55 1073 / 2791 (38.45%) 1434	39 / 2800 (1.39%) 41 35 / 2800 (1.25%) 36 18 / 2800 (0.64%) 18 433 / 2800 (15.46%) 522	
influenza like illness alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) malaise alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) mucosal inflammation	141 / 2791 (5.05%) 180 88 / 2791 (3.15%) 109	112 / 2800 (4.00%) 152 29 / 2800 (1.04%) 29	

<p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>72 / 2791 (2.58%)</p> <p>90</p>	<p>21 / 2800 (0.75%)</p> <p>32</p>	
<p>oedema peripheral</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>169 / 2791 (6.06%)</p> <p>200</p>	<p>103 / 2800 (3.68%)</p> <p>119</p>	
<p>pain</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>60 / 2791 (2.15%)</p> <p>64</p>	<p>53 / 2800 (1.89%)</p> <p>58</p>	
<p>peripheral swelling</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>51 / 2791 (1.83%)</p> <p>58</p>	<p>53 / 2800 (1.89%)</p> <p>61</p>	
<p>pyrexia</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>227 / 2791 (8.13%)</p> <p>299</p>	<p>114 / 2800 (4.07%)</p> <p>130</p>	
<p>Reproductive system and breast disorders</p> <p>breast pain</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>95 / 2791 (3.40%)</p> <p>104</p>	<p>120 / 2800 (4.29%)</p> <p>133</p>	
<p>erectile dysfunction</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[13]</p> <p>occurrences (all)</p>	<p>1 / 21 (4.76%)</p> <p>1</p>	<p>0 / 15 (0.00%)</p> <p>0</p>	
<p>vaginal discharge</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[14]</p> <p>occurrences (all)</p>	<p>26 / 2770 (0.94%)</p> <p>27</p>	<p>39 / 2785 (1.40%)</p> <p>42</p>	
<p>vulvovaginal dryness</p> <p>alternative dictionary used: MedDRA 23.0</p>			

subjects affected / exposed ^[15] occurrences (all)	78 / 2770 (2.82%) 80	117 / 2785 (4.20%) 127	
Respiratory, thoracic and mediastinal disorders cough alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	337 / 2791 (12.07%) 407	193 / 2800 (6.89%) 228	
dyspnoea alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	139 / 2791 (4.98%) 154	77 / 2800 (2.75%) 86	
epistaxis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	49 / 2791 (1.76%) 52	8 / 2800 (0.29%) 10	
nasal congestion alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	34 / 2791 (1.22%) 37	29 / 2800 (1.04%) 33	
oropharyngeal pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	115 / 2791 (4.12%) 142	76 / 2800 (2.71%) 91	
pneumonitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	36 / 2791 (1.29%) 36	10 / 2800 (0.36%) 10	
productive cough alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	45 / 2791 (1.61%) 53	25 / 2800 (0.89%) 28	
rhinitis allergic alternative dictionary used: MedDRA 23.0			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>rhinorrhoea</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>40 / 2791 (1.43%)</p> <p>41</p> <p>29 / 2791 (1.04%)</p> <p>31</p>	<p>40 / 2800 (1.43%)</p> <p>42</p> <p>15 / 2800 (0.54%)</p> <p>16</p>	
<p>Psychiatric disorders</p> <p>anxiety</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>depression</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>insomnia</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>81 / 2791 (2.90%)</p> <p>84</p> <p>134 / 2791 (4.80%)</p> <p>142</p> <p>208 / 2791 (7.45%)</p> <p>251</p>	<p>113 / 2800 (4.04%)</p> <p>116</p> <p>116 / 2800 (4.14%)</p> <p>120</p> <p>218 / 2800 (7.79%)</p> <p>246</p>	
<p>Investigations</p> <p>alanine aminotransferase increased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>aspartate aminotransferase increased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>blood alkaline phosphatase increased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>blood creatinine increased</p> <p>alternative dictionary used: MedDRA 23.0</p>	<p>265 / 2791 (9.49%)</p> <p>345</p> <p>257 / 2791 (9.21%)</p> <p>323</p> <p>83 / 2791 (2.97%)</p> <p>98</p>	<p>119 / 2800 (4.25%)</p> <p>149</p> <p>106 / 2800 (3.79%)</p> <p>122</p> <p>47 / 2800 (1.68%)</p> <p>56</p>	

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>gamma-glutamyltransferase increased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>weight decreased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>weight increased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>277 / 2791 (9.92%)</p> <p>396</p> <p>70 / 2791 (2.51%)</p> <p>80</p> <p>79 / 2791 (2.83%)</p> <p>88</p> <p>29 / 2791 (1.04%)</p> <p>32</p>	<p>17 / 2800 (0.61%)</p> <p>22</p> <p>24 / 2800 (0.86%)</p> <p>28</p> <p>19 / 2800 (0.68%)</p> <p>20</p> <p>46 / 2800 (1.64%)</p> <p>47</p>	
<p>Injury, poisoning and procedural complications</p> <p>contusion</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>fall</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>procedural pain</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>42 / 2791 (1.50%)</p> <p>51</p> <p>52 / 2791 (1.86%)</p> <p>61</p> <p>73 / 2791 (2.62%)</p> <p>78</p>	<p>37 / 2800 (1.32%)</p> <p>38</p> <p>36 / 2800 (1.29%)</p> <p>43</p> <p>53 / 2800 (1.89%)</p> <p>64</p>	
<p>Cardiac disorders</p> <p>palpitations</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>54 / 2791 (1.93%)</p> <p>62</p>	<p>20 / 2800 (0.71%)</p> <p>22</p>	
Nervous system disorders			

dizziness alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	274 / 2791 (9.82%) 333	158 / 2800 (5.64%) 188	
dysgeusia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	103 / 2791 (3.69%) 121	8 / 2800 (0.29%) 8	
headache alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	482 / 2791 (17.27%) 809	359 / 2800 (12.82%) 553	
memory impairment alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	29 / 2791 (1.04%) 32	22 / 2800 (0.79%) 22	
neuropathy alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	193 / 2791 (6.92%) 221	203 / 2800 (7.25%) 234	
taste disorder alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	36 / 2791 (1.29%) 36	4 / 2800 (0.14%) 4	
Blood and lymphatic system disorders			
anaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	634 / 2791 (22.72%) 862	88 / 2800 (3.14%) 113	
leukopenia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	1026 / 2791 (36.76%) 1706	171 / 2800 (6.11%) 244	
lymphopenia			

alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	372 / 2791 (13.33%) 527	94 / 2800 (3.36%) 118	
neutropenia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	1246 / 2791 (44.64%) 2316	140 / 2800 (5.00%) 214	
thrombocytopenia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	341 / 2791 (12.22%) 528	39 / 2800 (1.39%) 48	
Ear and labyrinth disorders vertigo alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	70 / 2791 (2.51%) 93	47 / 2800 (1.68%) 55	
Eye disorders dry eye alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) lacrimation increased alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) vision blurred alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	71 / 2791 (2.54%) 76 137 / 2791 (4.91%) 158 46 / 2791 (1.65%) 52	28 / 2800 (1.00%) 31 10 / 2800 (0.36%) 10 24 / 2800 (0.86%) 25	
Gastrointestinal disorders abdominal distension alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) abdominal pain	75 / 2791 (2.69%) 90	27 / 2800 (0.96%) 28	

<p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>945 / 2791 (33.86%)</p> <p>1974</p>	<p>226 / 2800 (8.07%)</p> <p>275</p>	
<p>constipation</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>288 / 2791 (10.32%)</p> <p>377</p>	<p>142 / 2800 (5.07%)</p> <p>161</p>	
<p>diarrhoea</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2294 / 2791 (82.19%)</p> <p>11663</p>	<p>199 / 2800 (7.11%)</p> <p>288</p>	
<p>dry mouth</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>94 / 2791 (3.37%)</p> <p>103</p>	<p>25 / 2800 (0.89%)</p> <p>27</p>	
<p>dyspepsia</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>205 / 2791 (7.35%)</p> <p>264</p>	<p>61 / 2800 (2.18%)</p> <p>66</p>	
<p>flatulence</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>84 / 2791 (3.01%)</p> <p>95</p>	<p>11 / 2800 (0.39%)</p> <p>12</p>	
<p>gastritis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>58 / 2791 (2.08%)</p> <p>65</p>	<p>31 / 2800 (1.11%)</p> <p>34</p>	
<p>gastrooesophageal reflux disease</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>74 / 2791 (2.65%)</p> <p>76</p>	<p>45 / 2800 (1.61%)</p> <p>47</p>	
<p>haemorrhoids</p> <p>alternative dictionary used: MedDRA 23.0</p>			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>mouth ulceration</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>nausea</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>68 / 2791 (2.44%)</p> <p>82</p> <p>39 / 2791 (1.40%)</p> <p>48</p> <p>779 / 2791 (27.91%)</p> <p>1203</p>	<p>28 / 2800 (1.00%)</p> <p>28</p> <p>3 / 2800 (0.11%)</p> <p>3</p> <p>222 / 2800 (7.93%)</p> <p>274</p>	
<p>stomatitis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>toothache</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>vomiting</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>154 / 2791 (5.52%)</p> <p>212</p> <p>49 / 2791 (1.76%)</p> <p>55</p> <p>454 / 2791 (16.27%)</p> <p>744</p>	<p>30 / 2800 (1.07%)</p> <p>39</p> <p>42 / 2800 (1.50%)</p> <p>50</p> <p>117 / 2800 (4.18%)</p> <p>144</p>	
<p>Hepatobiliary disorders</p> <p>hepatic steatosis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>41 / 2791 (1.47%)</p> <p>42</p>	<p>35 / 2800 (1.25%)</p> <p>35</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>alopecia</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>dermatitis</p> <p>alternative dictionary used: MedDRA 23.0</p>	<p>254 / 2791 (9.10%)</p> <p>266</p>	<p>53 / 2800 (1.89%)</p> <p>53</p>	

subjects affected / exposed	28 / 2791 (1.00%)	11 / 2800 (0.39%)
occurrences (all)	31	13
dry skin		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	102 / 2791 (3.65%)	48 / 2800 (1.71%)
occurrences (all)	108	51
eczema		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	29 / 2791 (1.04%)	28 / 2800 (1.00%)
occurrences (all)	32	31
erythema		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	38 / 2791 (1.36%)	26 / 2800 (0.93%)
occurrences (all)	43	28
hyperhidrosis		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	29 / 2791 (1.04%)	32 / 2800 (1.14%)
occurrences (all)	33	34
nail disorder		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	43 / 2791 (1.54%)	4 / 2800 (0.14%)
occurrences (all)	45	4
night sweats		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	40 / 2791 (1.43%)	28 / 2800 (1.00%)
occurrences (all)	43	31
onychoclasia		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	46 / 2791 (1.65%)	7 / 2800 (0.25%)
occurrences (all)	54	7
pruritus		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	219 / 2791 (7.85%)	110 / 2800 (3.93%)
occurrences (all)	298	121

rash alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	272 / 2791 (9.75%) 332	106 / 2800 (3.79%) 132	
Renal and urinary disorders dysuria alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	46 / 2791 (1.65%) 53	25 / 2800 (0.89%) 29	
Endocrine disorders hypothyroidism alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	28 / 2791 (1.00%) 29	34 / 2800 (1.21%) 34	
Musculoskeletal and connective tissue disorders arthralgia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	571 / 2791 (20.46%) 705	876 / 2800 (31.29%) 1117	
arthritis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	9 / 2791 (0.32%) 10	29 / 2800 (1.04%) 33	
back pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	223 / 2791 (7.99%) 277	271 / 2800 (9.68%) 317	
bone pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	62 / 2791 (2.22%) 75	93 / 2800 (3.32%) 102	
joint range of motion decreased alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	24 / 2791 (0.86%) 35	29 / 2800 (1.04%) 40	

joint stiffness		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	22 / 2791 (0.79%)	56 / 2800 (2.00%)
occurrences (all)	25	59
muscle spasms		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	134 / 2791 (4.80%)	100 / 2800 (3.57%)
occurrences (all)	180	121
muscular weakness		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	29 / 2791 (1.04%)	16 / 2800 (0.57%)
occurrences (all)	31	16
musculoskeletal chest pain		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	70 / 2791 (2.51%)	72 / 2800 (2.57%)
occurrences (all)	77	76
musculoskeletal pain		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	111 / 2791 (3.98%)	154 / 2800 (5.50%)
occurrences (all)	120	170
musculoskeletal stiffness		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	32 / 2791 (1.15%)	33 / 2800 (1.18%)
occurrences (all)	34	37
myalgia		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	167 / 2791 (5.98%)	163 / 2800 (5.82%)
occurrences (all)	193	185
neck pain		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	48 / 2791 (1.72%)	59 / 2800 (2.11%)
occurrences (all)	49	64
osteopenia		
alternative dictionary used: MedDRA 23.0		

subjects affected / exposed	30 / 2791 (1.07%)	32 / 2800 (1.14%)	
occurrences (all)	30	32	
osteoporosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	45 / 2791 (1.61%)	71 / 2800 (2.54%)	
occurrences (all)	45	75	
pain in extremity			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	245 / 2791 (8.78%)	274 / 2800 (9.79%)	
occurrences (all)	292	354	
Infections and infestations			
bronchitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	42 / 2791 (1.50%)	40 / 2800 (1.43%)	
occurrences (all)	50	44	
cellulitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	37 / 2791 (1.33%)	28 / 2800 (1.00%)	
occurrences (all)	43	31	
conjunctivitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	55 / 2791 (1.97%)	30 / 2800 (1.07%)	
occurrences (all)	63	34	
gastroenteritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	73 / 2791 (2.62%)	32 / 2800 (1.14%)	
occurrences (all)	84	36	
herpes zoster			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	34 / 2791 (1.22%)	39 / 2800 (1.39%)	
occurrences (all)	34	39	
influenza			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	110 / 2791 (3.94%)	102 / 2800 (3.64%)
occurrences (all)	139	135
nasopharyngitis		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	231 / 2791 (8.28%)	186 / 2800 (6.64%)
occurrences (all)	324	285
oral herpes		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	29 / 2791 (1.04%)	8 / 2800 (0.29%)
occurrences (all)	34	9
pharyngitis		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	26 / 2791 (0.93%)	29 / 2800 (1.04%)
occurrences (all)	29	33
pneumonia		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	45 / 2791 (1.61%)	19 / 2800 (0.68%)
occurrences (all)	46	19
sinusitis		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	69 / 2791 (2.47%)	51 / 2800 (1.82%)
occurrences (all)	76	67
skin infection		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	33 / 2791 (1.18%)	23 / 2800 (0.82%)
occurrences (all)	36	26
upper respiratory tract infection		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	280 / 2791 (10.03%)	214 / 2800 (7.64%)
occurrences (all)	393	323
urinary tract infection		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	278 / 2791 (9.96%)	167 / 2800 (5.96%)
occurrences (all)	368	235

vaginal infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed ^[16] occurrences (all)	30 / 2770 (1.08%) 37	18 / 2785 (0.65%) 21	
viral infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	28 / 2791 (1.00%) 32	14 / 2800 (0.50%) 15	
vulvovaginal candidiasis alternative dictionary used: MedDRA 23.0 subjects affected / exposed ^[17] occurrences (all)	29 / 2770 (1.05%) 33	20 / 2785 (0.72%) 31	
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	312 / 2791 (11.18%) 352	54 / 2800 (1.93%) 57	
dehydration alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	33 / 2791 (1.18%) 39	7 / 2800 (0.25%) 7	
hypercalcaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	49 / 2791 (1.76%) 58	32 / 2800 (1.14%) 42	
hypercholesterolaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	48 / 2791 (1.72%) 53	61 / 2800 (2.18%) 67	
hyperglycaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	37 / 2791 (1.33%) 51	43 / 2800 (1.54%) 53	
hypertriglyceridaemia alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	67 / 2791 (2.40%)	45 / 2800 (1.61%)
occurrences (all)	82	63
hyperuricaemia		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	33 / 2791 (1.18%)	13 / 2800 (0.46%)
occurrences (all)	44	14
hypoalbuminaemia		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	30 / 2791 (1.07%)	12 / 2800 (0.43%)
occurrences (all)	39	17
hypokalaemia		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	105 / 2791 (3.76%)	22 / 2800 (0.79%)
occurrences (all)	126	31
vitamin d deficiency		
alternative dictionary used: MedDRA 23.0		
subjects affected / exposed	29 / 2791 (1.04%)	33 / 2800 (1.18%)
occurrences (all)	33	37

Notes:

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[17] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 October 2017	Safety management updates including toxicity dose adjustment guidance for ALT increases; exclusion of participants with a history of venous thromboembolism (VTE); updates to protocol selection criteria to better align with global clinical practice
29 June 2018	Increase in sample size from 3580 to 4580 participants; exclusion of participants with inflammatory breast cancer; recurrence tissue biomarker sample changed to mandatory for participants that undergo biopsy; updated to collect SAEs in both arms regardless of causality or relatedness through year 5; added section on safety monitoring for VTE
19 December 2018	Updated the ITT population to include participants in Cohort 1 and Cohort 2; modified VTE safety monitoring language including the addition of Appendix 12 guidance for management of VTE while on study; included AST in the hepatic function safety monitoring; number of events required at final IDFS was updated from approximately 345 to approximately 390 from across Cohort 1 and Cohort 2 to yield approximately 85% statistical power
25 June 2019	Update on the timing of the efficacy interim analyses to ensure the data are sufficiently mature; added interstitial lung disease (ILD)/pneumonitis as a new adverse drug reaction; added safety monitoring guidance related to ILD/pneumonitis
18 September 2019	Changed protocol language from 'capsules' to 'tablets or capsules' to allow for supply chain planning in the event the study switches from capsules formulation to tablets

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported