Clinical trial results:
COMPLEEMENT-1: An open-label, multicenter, Phase IIIb study to assess the safety and efficacy of ribociclib (LEE011) in combination with letrozole for the treatment of men and pre/postmenopausal women with hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (aBC) with no prior hormonal therapy for advanced disease

Summary

EudraCT number	2016-003467-19
Trial protocol	BE GB NL HU BG PT GR SK IT CZ AT ES DK NO PL FI SI RO LU
Global end of trial date	09 November 2022

Results information

Result version number	v1 (current)
This version publication date	12 October 2023
First version publication date	12 October 2023

Trial information

Trial identification

Sponsor protocol code	CLEE011A2404

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02941926
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus,, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety and tolerability of ribociclib + letrozole in men and pre/postmenopausal women with HR+, HER2- aBC who received no prior hormonal therapy for advanced disease.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 25
Country: Number of subjects enrolled	Austria: 30
Country: Number of subjects enrolled	Belgium: 228
Country: Number of subjects enrolled	Bulgaria: 52
Country: Number of subjects enrolled	Canada: 251
Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	Czechia: 65
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	Finland: 22
Country: Number of subjects enrolled	France: 306
Country: Number of subjects enrolled	Greece: 29
Country: Number of subjects enrolled	Hong Kong: 14
Country: Number of subjects enrolled	Hungary: 40
Country: Number of subjects enrolled	India: 103
Country: Number of subjects enrolled	Israel: 42
Country: Number of subjects enrolled	Italy: 554
Country: Number of subjects enrolled	Jordan: 20
Country: Number of subjects enrolled	Lebanon: 17
Country: Number of subjects enrolled	Malaysia: 28

Country: Number of subjects enrolled	Mexico: 17
Country: Number of subjects enrolled	Netherlands: 130
Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Oman: 2
Country: Number of subjects enrolled	Panama: 4
Country: Number of subjects enrolled	Philippines: 14
Country: Number of subjects enrolled	Poland: 64
Country: Number of subjects enrolled	Portugal: 53
Country: Number of subjects enrolled	Russian Federation: 129
Country: Number of subjects enrolled	Saudi Arabia: 10
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	Slovenia: 33
Country: Number of subjects enrolled	Spain: 526
Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	Thailand: 17
Country: Number of subjects enrolled	United Kingdom: 139
Country: Number of subjects enrolled	United States: 208
Worldwide total number of subjects	3246
EEA total number of subjects	2178

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)	2173
From 65 to 84 years	1049
85 years and over	24

Subject disposition

Recruitment

Recruitment details:

Core Phase was conducted across 514 centers in 38 countries.
Extension Phase was conducted across 189 centers in 25 countries.

Pre-assignment

Screening details:

A total of 3694 participants were screened in this study of which 3246 participants were enrolled in the study.

Period 1

Period 1 title	Core Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ribociclib + letrozole + goserelin/leuprolide

Arm description:

Participants received ribociclib (orally taken, 3 weeks on/1 week off) in combination with letrozole (orally taken once daily). For men and premenopausal women, either goserelin was given as an injectable subcutaneous implant or leuprolide was given as an intramuscular injection.

Arm type	Experimental
Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribociclib 200 mg tablets were centrally supplied to the investigators and administered orally once a day on days 1-21 of each 28-day cycle at a starting dose of 600 mg daily.

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

Dosage and administration details:

Letrozole was procured locally and administered orally once a day on a continuous daily schedule at a dose of 2.5 mg.

Investigational medicinal product name	Goserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Subcutaneous use

Dosage and administration details:

Goserelin was procured locally and administered in men and premenopausal women as an injectable subcutaneous implant administered on day 1 starting at Cycle 1 and then every 28 days at a dose of 3.6 mg.

Investigational medicinal product name	Leuprolide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection

Routes of administration	Intramuscular use

Dosage and administration details:

Leuprolide was procured locally and administered in men and premenopausal women as an injectable intramuscular depot administered on day 1 starting at Cycle 1 and then every 28 days at a dose of 7.5 mg.

Number of subjects in period 1	Ribociclib + letrozole + goserelin/leuprolide
Started	3246
Completed	1301
Not completed	1945
Adverse event, serious fatal	46
Physician decision	112
Adverse event, non-fatal	504
Technical problems	5
Protocol deviation	34
Progressive disease	1109
Lost to follow-up	8
Subject/guardian decision	127

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ribociclib + letrozole + goserelin/leuprolide

Arm description:

Participants received ribociclib (orally taken, 3 weeks on/1 week off) in combination with letrozole (orally taken once daily). For men and premenopausal women, either goserelin was given as an injectable subcutaneous implant or leuprolide was given as an intramuscular injection.

Arm type	Experimental
Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribociclib 200 mg tablets were centrally supplied to the investigators and administered orally once a day on days 1-21 of each 28-day cycle at a starting dose of 600 mg daily.

Investigational medicinal product name	Leuprolide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Leuprolide was procured locally and administered in men and premenopausal women as an injectable intramuscular depot administered on day 1 starting at Cycle 1 and then every 28 days at a dose of 7.5 mg

Investigational medicinal product name	Goserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Subcutaneous use

Dosage and administration details:

Goserelin was procured locally and administered in men and premenopausal women as an injectable subcutaneous implant administered on day 1 starting at Cycle 1 and then every 28 days at a dose of 3.6 mg.

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

Dosage and administration details:

Letrozole was procured locally and administered orally once a day on a continuous daily schedule at a dose of 2.5 mg.

Number of subjects in period 2[1]	Ribociclib + letrozole + goserelin/leuprolide
Started	413
Completed	112
Not completed	301
Adverse event, serious fatal	6
Physician decision	155
Adverse event, non-fatal	13
Progressive disease	115
Subject/guardian decision	12

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only patients who were deriving benefit at the end of the Core phase and ribociclib was not approved or available and reimbursed, were transitioned to the Extension Phase

Baseline characteristics

Reporting groups	
Reporting group title	Ribociclib + letrozole + goserelin/leuprolide
Reporting group description:	
Participants received ribociclib (orally taken, 3 weeks on/1 week off) in combination with letrozole (orally taken once daily). For men and premenopausal women, either goserelin was given as an injectable subcutaneous implant or leuprolide was given as an intramuscular injection.	

Reporting group values	Ribociclib + letrozole + goserelin/leuprolide	Total	
Number of subjects	3246	3246	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2173	2173	
From 65-84 years	1049	1049	
85 years and over	24	24	
Age Continuous			
Units: Years			
arithmetic mean	58.1		
standard deviation	± 12.22	-	
Sex: Female, Male			
Units: Participants			
Female	3207	3207	
Male	39	39	
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	2553	2553	
Unknown	284	284	
Asian	227	227	
Other	134	134	
Black	29	29	
Native American	18	18	
Pacific Islander	1	1	

End points

End points reporting groups

Reporting group title	Ribociclib + letrozole + goserelin/leuprolide

Reporting group description:

Participants received ribociclib (orally taken, 3 weeks on/1 week off) in combination with letrozole (orally taken once daily). For men and premenopausal women, either goserelin was given as an injectable subcutaneous implant or leuprolide was given as an intramuscular injection.

Reporting group title	Ribociclib + letrozole + goserelin/leuprolide

Reporting group description:

Participants received ribociclib (orally taken, 3 weeks on/1 week off) in combination with letrozole (orally taken once daily). For men and premenopausal women, either goserelin was given as an injectable subcutaneous implant or leuprolide was given as an intramuscular injection.

Primary: Number of participants with adverse events (AEs) and Serious AEs (SAEs) during treatment with ribociclib + letrozole in the Core phase

End point title	Number of participants with adverse events (AEs) and Serious AEs (SAEs) during treatment with ribociclib + letrozole in the Core phase[1]

End point description:

AEs were defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s).
SAEs were defined as meeting at least 1 of the following criteria: is fatal or life-threatening, Results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, is medically significant, requires inpatient hospitalization or prolongation of existing hospitalization. A SAE which caused death of the participant was considered as fatal SAE.
AEs were assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1 to 5 were used to characterize the severity of the Adverse Event. Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening and Grade 5: death related to AE.
A participant with multiple severity grades for an AE is only counted under the maximum grade.

End point type	Primary

End point timeframe:

From start of treatment up to 30 days after last treatment (for participants who did not enter to the Extension phase) or up to last treatment in the Core phase (for participants who entered the Extension phase), assessed up to approximately 33 months.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for the primary endpoint

End point values	Ribociclib + letrozole + goserelin/leuprolide			
Subject group type	Reporting group			
Number of subjects analysed	3246			
Units: Participants				
AEs- All grades	3203			
AEs- Grade ≥ 3	2461			
Treatment-related AEs (TRAEs)- All grades	3091			
TRAEs- Grade ≥ 3	2192			
SAEs- All grades	702			
SAEs- Grade ≥ 3	590			

Treatment-related SAEs (TRSAEs)- All grades	203			
TRSAEs- Grade ≥ 3	178			
Fatal SAEs- All grades	62			
Treatment-related Fatal SAEs- All grades	14			
AEs leading to discontinuation- All grades	528			
AEs leading to discontinuation- Grade ≥ 3	310			
TRAEs leading to discontinuation- All grades	418			
TRAEs leading to discontinuation-Grade ≥ 3	237			
AEs leading to dose modifications- All grades	2434			
AEs leading to dose modifications- Grade ≥ 3	2095			
TRAEs leading to dose modifications- All grades	2235			
TRAEs leading to dose modifications- Grade ≥ 3	1964			
AEs requiring additional therapy- All grades	2624			
AEs requiring additional therapy- Grade ≥ 3	844			
TRAEs requiring additional therapy- All grades	1613			
TRAEs requiring additional therapy- Grade ≥ 3	392			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) based on investigator's assessment (Core phase)

End point title	Clinical Benefit Rate (CBR) based on investigator's assessment (Core phase)

End point description:

Clinical benefit rate (CBR) is defined as the percentage of participants with a best overall response of complete response (CR), or partial response (PR) or an overall lesion response of stable disease (SD), lasting as per local review, for a duration of at least 24 weeks. CR, PR and SD are defined according to RECIST 1.1 based on investigator's assessment.
CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm
PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease.
95% CI was calculated using the exact binomial method.

End point type	Secondary

End point timeframe:

Up to approximately 33 months

End point values	Ribociclib + letrozole + goserelin/leuprolide			
Subject group type	Reporting group			
Number of subjects analysed	3246			
Units: Percentage of participants				
number (confidence interval 95%)	70.7 (69.1 to 72.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-Progression (TTP) based on investigator's assessment (Core phase)

End point title	Time-to-Progression (TTP) based on investigator's assessment (Core phase)

End point description:

Time to progression (TTP) is defined as time from date of start of treatment to the date of first documented progression or death due to underlying cancer. Participants with symptoms of rapidly progressing disease without radiologic evidence were classified as progression only when clear evidence of clinical deterioration was documented and/or patient discontinued due to 'Disease progression' or death due to study indication. When there was no documentation of radiologic evidence of progression, and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation was used as date of progression.
TTP was estimated using the Kaplan-Meier method. 95% CI of median was calculated according to Brookmeyer and Crowley method.

End point type	Secondary

End point timeframe:

Up to approximately 33 months

End point values	Ribociclib + letrozole + goserelin/leuprolide			
Subject group type	Reporting group			
Number of subjects analysed	3246			
Units: Months				
median (confidence interval 95%)	27.1 (25.7 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) based on investigator's assessment (Core phase)

End point title	Overall response rate (ORR) based on investigator's assessment (Core phase)

End point description:

Overall response rate (ORR) is defined as the percentage of participants with best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1 based on investigator's assessment.
CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm
PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
95% CI was calculated using the exact binomial method.

End point type	Secondary

End point timeframe:

Up to approximately 33 months

End point values	Ribociclib + letrozole + goserelin/leuprolide			
Subject group type	Reporting group			
Number of subjects analysed	3246			
Units: Percentage of participants				
number (confidence interval 95%)	29.3 (27.7 to 30.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Functional Assessment of Cancer Therapy - Breast (FACT-B) score (Core phase)

End point title	Change from baseline in Functional Assessment of Cancer Therapy - Breast (FACT-B) score (Core phase)

End point description:

Change from baseline in FACT-B scores was assessed. FACT-B is a self-report instrument that measures multidimensional quality of life (QOL) in patients with breast cancer. The FACT-B consists of 37 questions that address physical, social, emotional, and functional well-being, with specific questions relevant to women with breast cancer. Each item has a score range of 0 (Not at all) to 4 (Very much), with a total score ranging from 0-148. The higher the score, the better the QOL reported by the participant. A positive change from baseline indicates improvement in QoL.
Due to the nature of the questionnaire, only females were asked to complete this questionnaire.

End point type	Secondary

End point timeframe:

On Day 1 of Cycle 1, 2, 3, 4 ,5, 6, 8, 10, 12 and after that every 3 cycles, and End of treatment, assessed up to 33 months. Cycle=28 days

End point values	Ribociclib + letrozole + goserelin/leuprolide			
Subject group type	Reporting group			
Number of subjects analysed	1230			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1	0.2 (± 13.29)			
Cycle 3 Day 1	0.1 (± 13.72)			
Cycle 4 Day 1	-0.3 (± 14.90)			
Cycle 5 Day 1	0.0 (± 15.02)			
Cycle 6 Day 1	-0.8 (± 14.91)			
Cycle 8 Day 1	-0.9 (± 16.32)			
Cycle 10 Day 1	-1.2 (± 15.83)			
Cycle 12 Day 1	-1.6 (± 16.13)			
Cycle 15 Day 1	-2.0 (± 16.58)			
Cycle 18 Day 1	-2.0 (± 16.09)			
Cycle 21 Day 1	-2.0 (± 17.82)			
Cycle 24 Day 1	-3.0 (± 17.89)			
Cycle 27 Day 1	-2.7 (± 13.84)			
Cycle 30 Day 1	-2.0 (± 14.14)			
Cycle 33 Day 1	12.1 (± 21.10)			
End of Treatment	-4.1 (± 16.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with AEs and SAEs in the Extension phase

End point title	Number of participants with AEs and SAEs in the Extension phase

End point description:

AEs were defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s).
SAEs were defined as meeting at least 1 of the following criteria: is fatal or life-threatening, Results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, is medically significant, requires inpatient hospitalization or prolongation of existing hospitalization.
AEs were assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1 to 5 were used to characterize the severity of the Adverse Event. Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening and Grade 5: death related to AE.
A participant with multiple severity grades for an AE is only counted under the maximum grade.

End point type	Secondary

End point timeframe:

From first dose of treatment in the Extension phase up to 30 days after last dose of treatment, assessed up approximately 37.6 months

End point values	Ribociclib + letrozole + goserelin/leuprolide			
Subject group type	Reporting group			
Number of subjects analysed	413			
Units: Participants				
AEs- All grades	297			
AEs- Grade ≥ 3	159			
Treatment-related AEs (TRAEs)- All grades	221			
TRAEs- Grade ≥ 3	123			
SAEs- All grades	54			
SAEs- Grade ≥ 3	45			
Treatment-related SAEs (TRSAEs)- All grades	7			
TRSAEs- Grade ≥ 3	6			
Fatal SAEs- All grades	5			
Treatment-related Fatal SAEs- All grades	0			
AEs leading to discontinuation- All grades	17			
AEs leading to discontinuation- Grade ≥ 3	9			
TRAEs leading to discontinuation- All grades	7			
TRAEs leading to discontinuation-Grade ≥ 3	4			
AEs leading to dose modifications- All grades	185			
AEs leading to dose modifications- Grade ≥ 3	132			
TRAEs leading to dose modifications- All grades	134			
TRAEs leading to dose modifications- Grade ≥ 3	113			
AEs requiring additional therapy- All grades	186			
AEs requiring additional therapy- Grade ≥ 3	56			
TRAEs requiring additional therapy- All grades	47			
TRAEs requiring additional therapy- Grade ≥ 3	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical benefit (Extension phase)

End point title	Number of participants with clinical benefit (Extension phase)

End point description:

Clinical benefit as assessed by the Investigator during Extension phase

End point type	Secondary

End point timeframe:

On Day 1 of every 3 cycles, starting from Cycle 1 of the Extension phase until end of treatment, assessed up to 37.4 months. Cycle= 28 days

End point values	Ribociclib + letrozole + goserelin/leuprolide			
Subject group type	Reporting group			
Number of subjects analysed	413			
Units: Participants				
Cycle 1 Day 1	413			
Cycle 4 Day 1	386			
Cycle 7 Day 1	353			
Cycle 10 Day 1	323			
Cycle 13 Day 1	245			
Cycle 16 Day 1	200			
Cycle 19 Day 1	183			
Cycle 22 Day 1	118			
Cycle 25 Day 1	55			
Cycle 28 Day 1	51			
Cycle 31 Day 1	44			
Cycle 34 Day 1	32			
Cycle 37 Day 1	24			
Cycle 40 Day 1	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Core: First dose to 30 days after last treatment (non-Extension participants) or last treatment in the Core (Extension participants), assessed up to 33 months.
Extension: First dose to 30 days after last treatment, assessed up to approx. 37.6 months.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	All patients- Extension phase

Reporting group description:

AEs collected during the Extension phase (from first dose of treatment in the Extension phase up to 30 days after last dose of treatment)

Reporting group title	All patients- Core phase

Reporting group description:

AEs collected in the core phase of the study (up to 30 days after last treatment for participants who did not enter the Extension phase or up to last treatment in the Core phase for participants who entered the Extension phase)

Serious adverse events	All patients- Extension phase	All patients- Core phase	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 413 (13.08%)	702 / 3246 (21.63%)	
number of deaths (all causes)	5	74	
number of deaths resulting from adverse events	0	14	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma of the cervix			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 413 (0.24%)	6 / 3246 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer recurrent			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic cancer			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leiomyoma			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ependymoma			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of pleura			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Malignant neoplasm progression			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Malignant pleural effusion			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cancer			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			

subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (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			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein embolism			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 413 (0.00%)	6 / 3246 (0.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 413 (0.00%)	13 / 3246 (0.40%)	
occurrences causally related to treatment / all	0 / 0	3 / 14	
deaths causally related to treatment / all	0 / 0	1 / 4	
Gait disturbance			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 413 (0.00%)	5 / 3246 (0.15%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza like illness			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 413 (0.24%)	9 / 3246 (0.28%)	
occurrences causally related to treatment / all	0 / 1	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Malaise			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic mass			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organ failure			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema peripheral			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-existing condition improved			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenosis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 413 (0.24%)	25 / 3246 (0.77%)	
occurrences causally related to treatment / all	0 / 1	7 / 25	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sudden death			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Strangulated hernia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			

Menopause			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopause			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Colpocele			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast mass			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast pain			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 413 (0.48%)	45 / 3246 (1.39%)	
occurrences causally related to treatment / all	0 / 2	9 / 47	
deaths causally related to treatment / all	0 / 0	1 / 3	
Dyspnoea exertional			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 413 (0.24%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lung infiltration			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 413 (0.00%)	19 / 3246 (0.59%)	
occurrences causally related to treatment / all	0 / 0	6 / 19	
deaths causally related to treatment / all	0 / 0	0 / 2	
Oropharyngeal pain			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 413 (0.00%)	8 / 3246 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumomediastinum			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 413 (0.00%)	34 / 3246 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 39	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory gas exchange disorder			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 413 (0.24%)	8 / 3246 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 8	
deaths causally related to treatment / all	0 / 1	0 / 5	
Respiratory distress			
subjects affected / exposed	1 / 413 (0.24%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery stenosis			

subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apathy			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervousness			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device extrusion			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 413 (0.00%)	15 / 3246 (0.46%)	
occurrences causally related to treatment / all	0 / 0	12 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 413 (0.00%)	23 / 3246 (0.71%)	
occurrences causally related to treatment / all	0 / 0	19 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood bilirubin increased			
subjects affected / exposed	0 / 413 (0.00%)	10 / 3246 (0.31%)	
occurrences causally related to treatment / all	0 / 0	5 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Waist circumference increased			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 413 (0.00%)	6 / 3246 (0.18%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 413 (0.00%)	6 / 3246 (0.18%)	
occurrences causally related to treatment / all	0 / 0	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycoplasma test positive			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate decreased			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Electrocardiogram change			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biopsy liver abnormal			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			

subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 413 (0.24%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 413 (0.48%)	8 / 3246 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			

subjects affected / exposed	1 / 413 (0.24%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 413 (0.24%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation of wound			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 413 (0.00%)	10 / 3246 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation skin injury			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tibia fracture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning deliberate			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic valve incompetence			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Atrioventricular block complete			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 413 (0.00%)	7 / 3246 (0.22%)	
occurrences causally related to treatment / all	0 / 0	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 413 (0.24%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cor pulmonale			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Coronary artery stenosis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 413 (0.00%)	5 / 3246 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular dysfunction			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	1 / 413 (0.24%)	9 / 3246 (0.28%)	
occurrences causally related to treatment / all	1 / 1	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 2	
Coma			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral cyst			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dystonia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 413 (0.00%)	7 / 3246 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			

subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis recurrent laryngeal nerve			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petit mal epilepsy			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 413 (0.24%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 413 (0.00%)	6 / 3246 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial mass			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 413 (0.00%)	24 / 3246 (0.74%)	
occurrences causally related to treatment / all	0 / 0	17 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 413 (0.00%)	21 / 3246 (0.65%)	
occurrences causally related to treatment / all	0 / 0	16 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node pain			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			

subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 413 (0.00%)	9 / 3246 (0.28%)	
occurrences causally related to treatment / all	0 / 0	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 413 (0.24%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 413 (0.00%)	8 / 3246 (0.25%)	
occurrences causally related to treatment / all	0 / 0	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eyelid ptosis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amaurosis fugax			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 413 (0.24%)	16 / 3246 (0.49%)	
occurrences causally related to treatment / all	0 / 2	5 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain upper			

subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 413 (0.00%)	14 / 3246 (0.43%)	
occurrences causally related to treatment / all	0 / 0	7 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 413 (0.00%)	6 / 3246 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal obstruction			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 413 (0.00%)	6 / 3246 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 413 (0.24%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 413 (0.00%)	12 / 3246 (0.37%)	
occurrences causally related to treatment / all	0 / 0	7 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic artery aneurysm			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland calculus			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal stenosis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stomatitis			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 413 (0.48%)	31 / 3246 (0.96%)	
occurrences causally related to treatment / all	0 / 2	17 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 413 (0.24%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal ulcer			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	1 / 413 (0.24%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 413 (0.00%)	5 / 3246 (0.15%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 4	
Drug-induced liver injury			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 413 (0.00%)	5 / 3246 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disease			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatitis toxic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			

subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertension			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petechiae			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 413 (0.00%)	12 / 3246 (0.37%)	
occurrences causally related to treatment / all	0 / 0	4 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder necrosis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 413 (0.00%)	5 / 3246 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 413 (0.24%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal impairment			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular disorder			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
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			
Arthralgia			
subjects affected / exposed	0 / 413 (0.00%)	8 / 3246 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			

subjects affected / exposed	3 / 413 (0.73%)	21 / 3246 (0.65%)	
occurrences causally related to treatment / all	0 / 3	1 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 413 (0.00%)	7 / 3246 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rigidity			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 413 (0.00%)	6 / 3246 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 413 (0.00%)	9 / 3246 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 413 (0.24%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess intestinal			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholinitis			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 413 (0.24%)	10 / 3246 (0.31%)	
occurrences causally related to treatment / all	1 / 2	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 413 (0.00%)	9 / 3246 (0.28%)	
occurrences causally related to treatment / all	0 / 0	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gallbladder empyema			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 413 (0.00%)	5 / 3246 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fungal infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 413 (0.48%)	12 / 3246 (0.37%)	
occurrences causally related to treatment / all	0 / 2	2 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 413 (0.24%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			

subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia influenzal			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 413 (1.21%)	35 / 3246 (1.08%)	
occurrences causally related to treatment / all	1 / 7	8 / 37	
deaths causally related to treatment / all	0 / 1	0 / 3	
Post procedural infection			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 413 (0.00%)	3 / 3246 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Sepsis			
subjects affected / exposed	0 / 413 (0.00%)	12 / 3246 (0.37%)	
occurrences causally related to treatment / all	0 / 0	4 / 12	
deaths causally related to treatment / all	0 / 0	2 / 2	
Respiratory tract infection viral			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Spinal cord infection			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 413 (0.00%)	5 / 3246 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 413 (0.24%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 413 (0.00%)	5 / 3246 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 413 (0.24%)	17 / 3246 (0.52%)	
occurrences causally related to treatment / all	0 / 1	3 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			

subjects affected / exposed	1 / 413 (0.24%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	3 / 413 (0.73%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
COVID-19			
subjects affected / exposed	5 / 413 (1.21%)	0 / 3246 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypermagnesaemia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food intolerance			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	0 / 413 (0.00%)	5 / 3246 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 413 (0.00%)	2 / 3246 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 413 (0.00%)	8 / 3246 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 413 (0.00%)	4 / 3246 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 413 (0.00%)	9 / 3246 (0.28%)	
occurrences causally related to treatment / all	0 / 0	4 / 10	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypophosphataemia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mineral metabolism disorder			
subjects affected / exposed	0 / 413 (0.00%)	1 / 3246 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	All patients- Extension phase	All patients- Core phase	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	247 / 413 (59.81%)	3150 / 3246 (97.04%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 413 (2.42%)	523 / 3246 (16.11%)	
occurrences (all)	10	657	
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 413 (2.91%)	456 / 3246 (14.05%)	
occurrences (all)	13	566	
White blood cell count decreased			
subjects affected / exposed	21 / 413 (5.08%)	336 / 3246 (10.35%)	
occurrences (all)	35	665	
Neutrophil count decreased			
subjects affected / exposed	29 / 413 (7.02%)	623 / 3246 (19.19%)	
occurrences (all)	70	1670	
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 413 (0.73%)	217 / 3246 (6.69%)	
occurrences (all)	3	263	
Blood creatinine increased			
subjects affected / exposed	6 / 413 (1.45%)	199 / 3246 (6.13%)	
occurrences (all)	7	271	
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 413 (1.94%)	490 / 3246 (15.10%)	
occurrences (all)	9	519	
Hypertension			
subjects affected / exposed	11 / 413 (2.66%)	227 / 3246 (6.99%)	
occurrences (all)	13	272	
Nervous system disorders			
Headache			

subjects affected / exposed	20 / 413 (4.84%)	458 / 3246 (14.11%)	
occurrences (all)	26	635	
Dizziness			
subjects affected / exposed	13 / 413 (3.15%)	235 / 3246 (7.24%)	
occurrences (all)	14	277	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	13 / 413 (3.15%)	254 / 3246 (7.83%)	
occurrences (all)	19	455	
Neutropenia			
subjects affected / exposed	116 / 413 (28.09%)	1981 / 3246 (61.03%)	
occurrences (all)	294	5908	
Lymphopenia			
subjects affected / exposed	4 / 413 (0.97%)	165 / 3246 (5.08%)	
occurrences (all)	6	239	
Leukopenia			
subjects affected / exposed	23 / 413 (5.57%)	596 / 3246 (18.36%)	
occurrences (all)	38	1259	
Anaemia			
subjects affected / exposed	22 / 413 (5.33%)	597 / 3246 (18.39%)	
occurrences (all)	25	843	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 413 (2.91%)	627 / 3246 (19.32%)	
occurrences (all)	12	789	
Fatigue			
subjects affected / exposed	14 / 413 (3.39%)	756 / 3246 (23.29%)	
occurrences (all)	15	885	
Oedema peripheral			
subjects affected / exposed	2 / 413 (0.48%)	279 / 3246 (8.60%)	
occurrences (all)	2	320	
Pyrexia			
subjects affected / exposed	25 / 413 (6.05%)	393 / 3246 (12.11%)	
occurrences (all)	26	497	

Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	5 / 413 (1.21%)	237 / 3246 (7.30%)	
occurrences (all)	5	265	
Diarrhoea			
subjects affected / exposed	18 / 413 (4.36%)	684 / 3246 (21.07%)	
occurrences (all)	20	1019	
Constipation			
subjects affected / exposed	11 / 413 (2.66%)	553 / 3246 (17.04%)	
occurrences (all)	12	663	
Abdominal pain upper			
subjects affected / exposed	1 / 413 (0.24%)	216 / 3246 (6.65%)	
occurrences (all)	1	251	
Abdominal pain			
subjects affected / exposed	7 / 413 (1.69%)	213 / 3246 (6.56%)	
occurrences (all)	7	259	
Nausea			
subjects affected / exposed	21 / 413 (5.08%)	1160 / 3246 (35.74%)	
occurrences (all)	27	1628	
Vomiting			
subjects affected / exposed	18 / 413 (4.36%)	633 / 3246 (19.50%)	
occurrences (all)	19	1045	
Stomatitis			
subjects affected / exposed	4 / 413 (0.97%)	291 / 3246 (8.96%)	
occurrences (all)	4	364	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	10 / 413 (2.42%)	275 / 3246 (8.47%)	
occurrences (all)	10	303	
Cough			
subjects affected / exposed	10 / 413 (2.42%)	492 / 3246 (15.16%)	
occurrences (all)	11	585	
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	6 / 413 (1.45%)	374 / 3246 (11.52%)	
occurrences (all)	7	472	
Pruritus			
subjects affected / exposed	2 / 413 (0.48%)	431 / 3246 (13.28%)	
occurrences (all)	2	543	
Dry skin			
subjects affected / exposed	5 / 413 (1.21%)	228 / 3246 (7.02%)	
occurrences (all)	5	246	
Alopecia			
subjects affected / exposed	4 / 413 (0.97%)	638 / 3246 (19.65%)	
occurrences (all)	4	663	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 413 (0.48%)	274 / 3246 (8.44%)	
occurrences (all)	2	291	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	5 / 413 (1.21%)	192 / 3246 (5.91%)	
occurrences (all)	5	212	
Musculoskeletal pain			
subjects affected / exposed	1 / 413 (0.24%)	205 / 3246 (6.32%)	
occurrences (all)	1	231	
Bone pain			
subjects affected / exposed	9 / 413 (2.18%)	225 / 3246 (6.93%)	
occurrences (all)	10	256	
Back pain			
subjects affected / exposed	22 / 413 (5.33%)	426 / 3246 (13.12%)	
occurrences (all)	24	514	
Arthralgia			
subjects affected / exposed	38 / 413 (9.20%)	674 / 3246 (20.76%)	
occurrences (all)	43	893	
Pain in extremity			
subjects affected / exposed	14 / 413 (3.39%)	263 / 3246 (8.10%)	
occurrences (all)	16	320	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	7 / 413 (1.69%)	194 / 3246 (5.98%)	
occurrences (all)	10	237	
Urinary tract infection			
subjects affected / exposed	16 / 413 (3.87%)	195 / 3246 (6.01%)	
occurrences (all)	26	279	
Upper respiratory tract infection			
subjects affected / exposed	12 / 413 (2.91%)	191 / 3246 (5.88%)	
occurrences (all)	17	235	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 413 (1.69%)	401 / 3246 (12.35%)	
occurrences (all)	7	442	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2016	Premenopausal patients (receiving concomitant ovarian suppression with goserelin) were allowed to be included in the study, based on current treatment guidelines. Male patients entering the study were also required to use goserelin concurrently with ribociclib + letrozole based on the current standard of care in this patient population. The end of the Core Phase was defined as 18 months after LPFV. Secondary objectives and the associated end points for Extension Phase were stated. Dose modification guidelines were updated
16 August 2017	Expansion of another monthly-based dosing LHRH agonist (leuprolide) in addition to goserelin, based on NCCN Breast Cancer Guidelines 2017. Removal of requirement for prior anti-cancer therapy, 5 half-lives, washout period. Clarification of the sample size calculation: 3000 patients were planned to be enrolled in this study to detect rare AEs (frequency ~0.1%) with high probability.
24 September 2018	Updated the language regarding early study termination by the sponsor. Updated withdrawal of consent language with the new Global Data Protection Requirements. Updated the dose adjustment and management recommendations for QTcF prolongation, as analyses of preclinical and clinical data with ribociclib have demonstrated that ribociclib prolongs the QT interval in a concentration-dependent manner. Updated the list of prohibited medications during study treatment, and co-medication considerations. Updated the list of medications to be used with caution during study drug treatment period
23 January 2020	Updated safety information on ribociclib in alignment with LEE011 (Ribociclib) Investigator's Brochure (IB), Edition 14 (release date: 28-Nov-2019) and definition of the duration of the Extension Phase and transition plan for patients during and at the end of the study. Significant changes included: Addition of ribociclib dose adjustment and management recommendation for interstitial lung disease/pneumonitis, which was observed with CDK4/6 inhibitor treatment as a class effect; Addition of guidance to discontinue ribociclib if toxic epidermal necrolysis is diagnosed; Updated tables relating to hepatic and cardiac QTc monitoring; Updated the lists of prohibited medications and medications to be used with caution during study treatment; Updated the language regarding Extension Phase duration (defined as 18 months after LPLV of the Core Phase) and transition plan

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/ for complete trial results.

Notes: