Clinical trial results:
A national phase IIIb, multi-center, open label study for women and men with hormone-receptor positive, HER2-negative locally advanced or metastatic breast cancer treated with ribociclib (LEE011) in combination with letrozole RIBECCA RIBociclib for the trEatment of advanCed breast CAncer

Summary

EudraCT number	2016-002556-24
Trial protocol	DE
Global end of trial date	06 February 2020

Results information

Result version number	v2 (current)
This version publication date	30 August 2021
First version publication date	22 February 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CLEE011XDE01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03096847
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	06 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was the assessment of the clinical benefit rate (CBR) after 24 weeks for the total population and for cohorts A and B separately:
-To assess the CBR after 24 weeks for ribociclib (LEE011) in combination with letrozole among postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no prior treatment for advanced disease. (70% group) (Cohort A)
-To assess the CBR after 24 weeks for ribociclib (LEE011) in combination with letrozole and goserelin among pre-, and perimenopausal women who received no prior treatment for advanced disease as well as pre-, peri- and postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no more than 1 prior chemotherapy and 2 prior lines of endocrine therapy for advanced disease (30% group) (Cohort B)

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	24 October 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	Germany: 502
Worldwide total number of subjects	502
EEA total number of subjects	502

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)	256
From 65 to 84 years	240
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

504 part. entered study, but 2 of these participants were not treated. The full analysis set (FAS) is comprised of 504 part. minus 17 participants, whose data were removed because of inspection findings, to equal 487 part. This FAS includes 2 part. who entered the study but were not treated.

502 part. were treated and included in the safety set.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ribociclib + letrozole cohort A

Arm description:

postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.

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

Dosage and administration details:

postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.

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

Dosage and administration details:

postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.

Arm title	ribociclib + letrozole cohort B1

Arm description:

premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

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

Dosage and administration details:

premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

Investigational medicinal product name	Goserelin (for premenopausal patients)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Subcutaneous use

Dosage and administration details:

premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

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

Dosage and administration details:

premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

Arm title	ribociclib + letrozole cohort B2

Arm description:

premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

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

Dosage and administration details:

premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

Investigational medicinal product name	Goserelin (for premenopausal patients)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Subcutaneous use

Dosage and administration details:

premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

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

Dosage and administration details:

premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

Number of subjects in period 1	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2
Started	319	26	157
Full Analysis Set	307	26	154
Completed	100	6	19
Not completed	219	20	138
Adverse event, serious fatal	6	-	2
Physician decision	12	2	8
Consent withdrawn by subject	24	1	12
Adverse event, non-fatal	72	6	28
Non-compliance with study medication	1	-	-
Lost to follow-up	1	-	1
Progressive disease	97	10	78
New therapy for study indication	1	-	1
Protocol deviation	3	-	6
not specified	2	1	2

Baseline characteristics

Reporting groups	
Reporting group title	ribociclib + letrozole cohort A
Reporting group description:	
postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	
Reporting group title	ribociclib + letrozole cohort B1
Reporting group description:	
premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	
Reporting group title	ribociclib + letrozole cohort B2
Reporting group description:	
premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	

Reporting group values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2
Number of subjects	319	26	157
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	143	26	87
>=65 years	176	0	70
Age Continuous Units: Years			
arithmetic mean	65.7	46.5	62.8
standard deviation	± 10.1	± 4.9	± 12.8
Sex: Female, Male Units: Participants			
Female	315	26	156
Male	4	0	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	0
White	312	24	151
More than one race	1	0	3
Unknown or Not Reported	6	0	2

Reporting group values	Total		
Number of subjects	502		
Age Categorical Units: Participants			
<=18 years	0		
Between 18 and 65 years	256		

>=65 years	246		

Age Continuous Units: Years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: Participants			
Female	497		
Male	5		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	487		
More than one race	4		
Unknown or Not Reported	8		

End points

End points reporting groups

Reporting group title	ribociclib + letrozole cohort A
Reporting group description:	
postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	
Reporting group title	ribociclib + letrozole cohort B1
Reporting group description:	
premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	
Reporting group title	ribociclib + letrozole cohort B2
Reporting group description:	
premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	
Subject analysis set title	Total
Subject analysis set type	Safety analysis
Subject analysis set description:	
Cohort A and Cohort B combined	
Subject analysis set title	ribociclib + letrozole cohort B
Subject analysis set type	Full analysis
Subject analysis set description:	
premenopausal women or perimenopausal women or postmenopausal women, or men; naïve + pre-treated All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o.daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	
Subject analysis set title	Total
Subject analysis set type	Safety analysis
Subject analysis set description:	
Cohorts A, B1 and B2 combined	
Subject analysis set title	Total
Subject analysis set type	Safety analysis
Subject analysis set description:	
Cohort A and Cohort B combined	

Primary: Clinical Benefit Rate (CBR) in women and men with hormone receptor positiv, HER-2 negative breast cancer treated with ribocilib and letrozole

End point title	Clinical Benefit Rate (CBR) in women and men with hormone receptor positiv, HER-2 negative breast cancer treated with ribocilib and letrozole[1]
End point description:	
Clinical Benefit Rate (CBR) after 24 weeks of treatment as defined by RECIST 1.1 as percentage of patients with Complete Response (CR), Partial response (PR) or Stable disease (SD) lasting 24 weeks or longer as well as patients with Non-complete response, nonprogressive disease (NCRNPD).	
End point type	Primary
End point timeframe:	
At 24 weeks after last patient enrolled in trial	

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: Please note that the statistical significance test (test comparing groups) i.e., statistical

analysis was not applicable for this outcome measure, since the primary objective was to assess the rate (per cohort) and not to compare two or more treatment arms, as this was a non-randomized, single arm open label trial.

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	307	26	154	487
Units: Percentage of Participants				
number (confidence interval 95%)				
CBR by week 24(Confirmed (BOR))	63.2 (57.5 to 68.6)	57.7 (36.9 to 76.6)	56.5 (48.3 to 64.5)	60.8 (56.3 to 65.1)
CBR by week 24 (non-confirmed BOR)	71.7 (66.3 to 76.6)	69.2 (48.2 to 85.7)	64.3 (56.2 to 71.8)	69.2 (64.9 to 73.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) for different populations - Kaplan-Meier estimates (%, 95% CI)

End point title	Progression free survival (PFS) for different populations - Kaplan-Meier estimates (%, 95% CI)
End point description:	
PFS based on radiologic assessment by investigator using RECIST 1.1 criteria	
End point type	Secondary
End point timeframe:	
At week 24 , week 48 and week 72	

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	26	154	
Units: Percentage of Participants				
number (confidence interval 95%)				
Kaplan-Meier estimates (%, 95% CI) - Week 24	73.1 (67.3 to 77.9)	67.0 (44.7 to 82.0)	63.8 (55.2 to 71.3)	
Kaplan-Meier estimates (%, 95% CI) - Week 48	61.9 (55.7 to 67.5)	58.7 (36.8 to 75.2)	47.5 (38.7 to 55.7)	
Kaplan-Meier estimates (%, 95% CI) - week 72	54.5 (48.1 to 60.5)	49.6 (28.6 to 67.6)	39.3 (30.8 to 47.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) for different populations - Median time to progression or death with 95% CI [months]

End point title	Progression free survival (PFS) for different populations - Median time to progression or death with 95% CI [months]

End point description:

PFS based on radiologic assessment by investigator using RECIST 1.1 criteria

End point type	Secondary

End point timeframe:

Up to approximately month 25

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	26	154	
Units: Months				
median (confidence interval 95%)	21.8 (13.9 to 25.3)	16.5 (3.2 to 999)	8.8 (8.1 to 16.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Kaplan-Meier estimates (%, 95% CI)

End point title	Overall Survival (OS) - Kaplan-Meier estimates (%, 95% CI)

End point description:

Overall survival (OS) defined as the time from date of start of treatment to date of death due to any cause. For the Kaplan-Meier estimates (%, 95% CI), the probability of survival at week 24, 48 and 72 is reported below.

End point type	Secondary

End point timeframe:

At Week 24, Week 48 and Week 72

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	26	154	
Units: Percentage of Participants				
number (confidence interval 95%)				
Kaplan-Meier estimates (%, 95% CI) - Week 24	98.6 (96.4 to 99.5)	100.0 (100.0 to 100.0)	93.9 (88.5 to 96.8)	
Kaplan-Meier estimates (%, 95% CI) - Week 48	93.3 (89.7 to 95.7)	87.5 (66.1 to 95.8)	86.1 (79.2 to 90.8)	
Kaplan-Meier estimates (%, 95% CI) - Week 72	89.7 (85.5 to 92.7)	87.5 (66.1 to 95.8)	81.0 (73.5 to 86.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Median time to progression or death with 95% CI [months]

End point title	Overall Survival (OS) - Median time to progression or death with 95% CI [months]

End point description:

Overall survival (OS) defined as the time from date of start of treatment to date of death due to any cause.

End point type	Secondary

End point timeframe:

Up to approximatley 38 months

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	26	154	
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (30.9 to 999)	999 (31.0 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - number of censored participants and number of deaths

End point title	Overall Survival (OS) - number of censored participants and number of deaths

End point description:

Overall survival (OS) defined as the time from date of start of treatment to date of death due to any cause.

End point type	Secondary

End point timeframe:

Up to approximatley 38 months

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	26	154	
Units: Participants				
No. of censored (no death), n	240	17	94	
No. of events (deaths due to any cause), n	67	9	60	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) - Kaplan-Meier estimates (%, 95% CI)

End point title	Overall response rate (ORR) - Kaplan-Meier estimates (%, 95% CI)

End point description:

Overall response rate (ORR) is the best overall response (BOR) of complete response (CR) or partial response (PR) as defined by RECIST 1.1.

End point type	Secondary

End point timeframe:

At week 24

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	307	26	154	
Units: Percentage of Participants				
number (confidence interval 95%)				
ORR by week 24 - (BOR of CR or PR) (confirmed)	22.8 (18.2 to 27.9)	23.1 (9.0 to 43.6)	11.7 (7.1 to 17.8)	
ORR by week 24 - (BOR of CR or PR) (unconfirmed)	24.8 (20.0 to 30.0)	30.8 (14.3 to 51.8)	16.2 (10.8 to 23.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at week 24 of patient reported Quality of Life (QoL) via EORTC QLQ-C30

End point title	Change from baseline at week 24 of patient reported Quality of Life (QoL) via EORTC QLQ-C30

End point description:

The QLQ-C30 is the core questionnaire of the EORTC QLQ, which has been developed for the assessment of the health-related QOL of cancer patients participating in international clinical trials. Using a linear transformation to standardize the raw scores, all scores finally range from 0 to 100,

where a higher score represents a higher response level, e.g., a higher ("better") level of functioning (applies to the first 6 items, items 1 to 6), but a higher ("worse") level of symptoms (applies to the last 9 items, items 7 to 15). There is no aggregated total score, i.e., all scale scores were analyzed separately.

CfBaW24 = change from baseline at week 24

End point type	Secondary
End point timeframe:	
Change from Baseline to Week 24	

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	ribociclib + letrozole cohort B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	307	26	154	180
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Global health status-CfBaW24 (n=181,15,75,90)	8.8 (± 23.7)	11.7 (± 20.8)	5.0 (± 26.2)	6.1 (± 25.4)
Physical Functioning-CfBaW24 (n=183,15,75,90)	-3.1 (± 19.9)	-3.6 (± 10.7)	-2.2 (± 17.7)	-2.4 (± 16.7)
Role Functioning-CfBaW24 (n=182,15,75,90)	-6.6 (± 31.9)	-17 (± 21.8)	-1.3 (± 34.7)	-3.9 (± 33.3)
Emotional Functioning-CfBaW24 (n=182,15,75,90)	-9.6 (± 24.2)	-9.4 (± 25.0)	-3.6 (± 21.8)	-4.6 (± 22.4)
Cognitive Functioning-CfBaW24 (n=182,15,75,90)	2.7 (± 23.7)	2.2 (± 28.1)	1.1 (± 21.6)	1.3 (± 22.7)
Social Functioning-CfBaW24 (n=181,15,75,90)	-6.9 (± 27.9)	-16 (± 21.3)	-5.3 (± 31.3)	-7.0 (± 30.0)
Fatigue -CfBaW24 (n=182,15,75,90)	6.3 (± 25.9)	11.1 (± 20.6)	3.9 (± 27.1)	5.1 (± 26.1)
Nausea / Vomiting-CfBaW24 (n=182,15,75,90)	0.1 (± 16.7)	1.1 (± 22.2)	-4.9 (± 19.1)	-3.9 (± 19.7)
Pain-CfBaW24 (n=182,15,74,89)	13.2 (± 31.9)	15.6 (± 24.8)	9.0 (± 27.6)	10.1 (± 27.1)
Dyspnoea -CfBaW24 (n=182,15,75,90)	3.8 (± 32.4)	4.4 (± 21.3)	-5.3 (± 30.5)	-3.7 (± 29.3)
Insomnia-CfBaW24 (n=183, 15,75,90)	4.2 (± 33.2)	6.7 (± 31.4)	4.9 (± 32.7)	5.2 (± 32.3)
Appetite loss-CfBaW24 (n=181, 15, 74, 89)	11.2 (± 33.7)	6.7 (± 28.7)	1.4 (± 30.9)	2.2 (± 30.5)
Constipation-CfBaW24 (n=183,15,74,89)	-2.7 (± 26.6)	2.2 (± 26.6)	-3.6 (± 27.9)	-2.6 (± 27.6)
Diarrhea-CfBaW24 (n=182,15,74,89)	2.6 (± 24.6)	0.0 (± 45.4)	2.3 (± 27.2)	1.9 (± 30.7)
Financial Problems-CfBaW24 (n=179,15,73,88)	0.2 (± 27.7)	-4.4 (± 24.8)	-1.4 (± 25.1)	-1.9 (± 24.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported Quality of Life (QoL) via EORTC BR-23 - change from baseline at Week 24 (Cycle 7)

End point title	Patient reported Quality of Life (QoL) via EORTC BR-23 - change from baseline at Week 24 (Cycle 7)

End point description:

To evaluate health related quality of life (QoL) via EORTC BR-23. The scoring approach for the QLQ-BR23 is identical in principle to that for the function and symptom scales / single items of the QLQ-C30, i.e., all scores finally range from 0 to 100, where a higher score represents a higher response level, e.g., a higher ("better") level of functioning, (applies to the first 4 items, items 1 to 4) but a higher ("worse") level of symptoms (applies to the last 4 items, items 5 to 8).

CfBaC7 = change from baseline at cycle 7

End point type	Secondary

End point timeframe:

Baseline and Week 24 (Cycle 7)

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	ribociclib + letrozole cohort B
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	307	26	154	180
Units: Scores on a scale				
arithmetic mean (standard deviation)				
BODY IMAGE-CfBaC7 (n=167,15,72,87)	-1.5 (± 18.2)	-0.6 (± 22.2)	0.4 (± 22.7)	0.2 (± 22.5)
SEXUAL FUNCTIONING- CfBaC7 (n=120,13,60,73)	-1.1 (± 17.7)	0.0 (± 24.5)	0.8 (± 18.0)	0.7 (± 19.1)
SEXUAL ENJOYMENT- CfBaC7 (n=18,2,18,20)	-1.9 (± 31.3)	-17 (± 23.6)	7.4 (± 26.9)	5.0 (± 27.1)
FUTURE PERSPECTIVE-CfBaC7 (n=172,15,74,89)	-20 (± 33.4)	-24 (± 26.6)	-12 (± 26.2)	-14 (± 26.5)
SYSTEMATIC THERAPY-CfBaC7 (n=180,15,74,89)	-9.4 (± 16.6)	-13 (± 22.3)	-6.0 (± 14.9)	-7.1 (± 16.4)
BREAST SYMPTOMS- CfBaC7 (n=172,15,73,88)	3.3 (± 15.7)	8.3 (± 22.7)	0.9 (± 17.5)	2.2 (± 18.6)
ARM SYMPTOMS - CfBaC7 (n=175,15,74,89)	4.1 (± 21.1)	-1.5 (± 22.6)	-2.1 (± 18.1)	-2.0 (± 18.8)
HAIR LOSS -CfBaC7 (n=23, 2,14,16)	-22 (± 43.4)	-17 (± 23.6)	-14 (± 33.9)	-15 (± 32.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 10% deterioration in EORTC global health status

End point title	Time to 10% deterioration in EORTC global health status

End point description:

Time to 10% deterioration in the European Organisation for Research and Treatment of Cancer (EORTC) global health status

End point type	Secondary

End point timeframe:

up to approximately 10 months

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	307	26	154	487
Units: months				
median (confidence interval 95%)	3.3 (2.8 to 4.6)	3.7 (1.8 to 10.1)	2.8 (1.8 to 4.6)	3.0 (2.8 to 4.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAE)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAE)

End point description:

Adverse Events (AEs) were separated into TEAEs (defined as AEs occurring/worsening from first study drug
treatment until 30 days after the last study drug treatment) and AEs in the pre-/post-treatment period.

End point type	Secondary

End point timeframe:

Up to Week 72

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	319	26	157	
Units: Number of Participants				
Total AEs (i.e., Includes any type of AE.)	318	25	157	
Serious AEs	97	5	45	
Non-serious AEs	317	25	157	
AEs with suspected relationship to ribociclib	302	25	144	
AEs leading to discontinuation of ribociclib	76	7	38	
AEs with fatal outcome	6	0	6	

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths

End point description:

On treatment deaths were collected from FPFT up to 30 days after study drug discontinuation, for a maximum duration of 1150 days (approx 3.15 years). (Treatment duration ranged from 2 days to 1120 days). Deaths post treatment survival follow up were collected after the on- treatment period, up to approx. 3.15 years. Patients who didn't die during the on-treatment period and had not stopped study participation at the time of data cut-off (end of study) were censored.

End point type	Post-hoc

End point timeframe:

on-treatment deaths: up to approx 3.15 years; all deaths: approx 3.15 years

End point values	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	319	26	157	502
Units: Participants				
on-treatment deaths	6	0	6	12
Total deaths (n=307,26,154, 487)	67	9	60	136

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days, up to a maximum duration of 1150 days (approx. 3.15 years).(Treatment duration ranged from 2 days to 1120 days.)

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	22.1

Reporting groups

Reporting group title	Cohort B:pr, pe, po Male or Female naïve+pre-tr.

Reporting group description:

Cohort B:pr, pe, po Male or Female naïve+pre-tr.

Reporting group title	Cohort A:po male or Female

Reporting group description:

Cohort A:po male or Female

Reporting group title	Cohort B2:pr, pe, po Male or Female pre-tr.

Reporting group description:

Cohort B2:pr, pe, po Male or Female pre-tr.

Reporting group title	Total

Reporting group description:

Total

Reporting group title	Cohort B1:pr, pe Female naïve

Reporting group description:

Cohort B1:pr, pe Female naïve

Serious adverse events	Cohort B:pr, pe, po Male or Female naïve+pre-tr.	Cohort A:po male or Female	Cohort B2:pr, pe, po Male or Female pre-tr.
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 183 (27.32%)	97 / 319 (30.41%)	45 / 157 (28.66%)
number of deaths (all causes)	6	6	6
number of deaths resulting from adverse events	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BRONCHIAL CARCINOMA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CANCER PAIN			

subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLON CANCER			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	0 / 183 (0.00%)	2 / 319 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTASES TO BONE			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTASES TO SPINE			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL CELL CARCINOMA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA OF THE TONGUE			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR PAIN			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
CIRCULATORY COLLAPSE			

subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMPLICATION OF DEVICE INSERTION			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEATH			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
FATIGUE			
subjects affected / exposed	2 / 183 (1.09%)	0 / 319 (0.00%)	2 / 157 (1.27%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH			

DETERIORATION			
subjects affected / exposed	5 / 183 (2.73%)	2 / 319 (0.63%)	5 / 157 (3.18%)
occurrences causally related to treatment / all	2 / 5	1 / 3	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMPAIRED HEALING			
subjects affected / exposed	2 / 183 (1.09%)	1 / 319 (0.31%)	2 / 157 (1.27%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN			
subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	1 / 183 (0.55%)	6 / 319 (1.88%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	3 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
PELVIC PAIN			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			

subjects affected / exposed	3 / 183 (1.64%)	9 / 319 (2.82%)	3 / 157 (1.91%)
occurrences causally related to treatment / all	0 / 3	3 / 10	0 / 3
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 1
DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERVENTILATION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	3 / 183 (1.64%)	3 / 319 (0.94%)	3 / 157 (1.91%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
PNEUMONITIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 183 (0.55%)	7 / 319 (2.19%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	1 / 7	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
PULMONARY FIBROSIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			

subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANIC ATTACK			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SOMATIC SYMPTOM DISORDER			
subjects affected / exposed	0 / 183 (0.00%)	2 / 319 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
DEVICE LOOSENING			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 183 (0.55%)	5 / 319 (1.57%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	1 / 1	5 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 183 (0.55%)	3 / 319 (0.94%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	1 / 1	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD BILIRUBIN INCREASED			

subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOGLOBIN DECREASED			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
ACCIDENT			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANKLE FRACTURE			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CERVICAL VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FALL			

subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
subjects affected / exposed	0 / 183 (0.00%)	3 / 319 (0.94%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIP FRACTURE			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCISIONAL HERNIA			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JAW FRACTURE			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST-TRAUMATIC PAIN			

subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE ADHESION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROCEDURAL COMPLICATION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADIUS FRACTURE			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RIB FRACTURE			
subjects affected / exposed	0 / 183 (0.00%)	3 / 319 (0.94%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TIBIA FRACTURE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	2 / 183 (1.09%)	2 / 319 (0.63%)	2 / 157 (1.27%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRADYARRHYTHMIA			

subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBRAL ISCHAEMIA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 183 (0.00%)	2 / 319 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIZZINESS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			

subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MONOPLEGIA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARAESTHESIA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL NERVE LESION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 183 (2.19%)	4 / 319 (1.25%)	4 / 157 (2.55%)
occurrences causally related to treatment / all	10 / 12	10 / 11	10 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DISSEMINATED INTRAVASCULAR COAGULATION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			

subjects affected / exposed	3 / 183 (1.64%)	0 / 319 (0.00%)	2 / 157 (1.27%)
occurrences causally related to treatment / all	3 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
HYPERFIBRINOLYSIS			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEUKOPENIA			
subjects affected / exposed	0 / 183 (0.00%)	2 / 319 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
subjects affected / exposed	2 / 183 (1.09%)	2 / 319 (0.63%)	2 / 157 (1.27%)
occurrences causally related to treatment / all	1 / 2	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 183 (0.00%)	3 / 319 (0.94%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 3	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN LOWER			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL HAEMORRHAGE			

subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
subjects affected / exposed	0 / 183 (0.00%)	2 / 319 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	1 / 183 (0.55%)	3 / 319 (0.94%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS			
subjects affected / exposed	0 / 183 (0.00%)	3 / 319 (0.94%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS			
subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
INTESTINAL STRANGULATION			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	2 / 183 (1.09%)	7 / 319 (2.19%)	2 / 157 (1.27%)
occurrences causally related to treatment / all	0 / 3	2 / 8	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
VOMITING			

subjects affected / exposed	0 / 183 (0.00%)	3 / 319 (0.94%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILE DUCT STENOSIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BILIARY COLIC			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLELITHIASIS			
subjects affected / exposed	0 / 183 (0.00%)	2 / 319 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	1 / 183 (0.55%)	5 / 319 (1.57%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	1 / 1	6 / 6	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC CIRRHOSIS			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATOTOXICITY			

subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JAUNDICE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 183 (0.55%)	5 / 319 (1.57%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
HAEMATURIA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KIDNEY CONGESTION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL DISORDER			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			
subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL IMPAIRMENT			

subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETERIC STENOSIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETEROLITHIASIS			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY INCONTINENCE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY RETENTION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT OBSTRUCTION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
HYPERTHYROIDISM			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

BACK PAIN			
subjects affected / exposed	0 / 183 (0.00%)	2 / 319 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE LESION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE PAIN			
subjects affected / exposed	2 / 183 (1.09%)	2 / 319 (0.63%)	2 / 157 (1.27%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FLANK PAIN			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR SPINAL STENOSIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MOBILITY DECREASED			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEITIS			

subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOARTHRITIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEONECROSIS OF JAW			
subjects affected / exposed	0 / 183 (0.00%)	2 / 319 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 183 (0.00%)	2 / 319 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL PAIN			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL ABSCESS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABSCESS JAW			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATYPICAL PNEUMONIA			

subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS INFECTIVE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYSTITIS			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYSTITIS ESCHERICHIA			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEVICE RELATED INFECTION			
subjects affected / exposed	2 / 183 (1.09%)	0 / 319 (0.00%)	2 / 157 (1.27%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
DIVERTICULITIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMPHYSEMATOUS CHOLECYSTITIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYSIPELAS			

subjects affected / exposed	0 / 183 (0.00%)	3 / 319 (0.94%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA INFECTION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE INFECTION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL INFECTION			
subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HELICOBACTER GASTRITIS			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MASTITIS			

subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	2 / 183 (1.09%)	8 / 319 (2.51%)	2 / 157 (1.27%)
occurrences causally related to treatment / all	1 / 2	2 / 8	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 2	1 / 1
PROTEUS INFECTION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY SYNCYTIAL VIRUS INFECTION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 183 (0.00%)	3 / 319 (0.94%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UROSEPSIS			

subjects affected / exposed	0 / 183 (0.00%)	2 / 319 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	1 / 183 (0.55%)	1 / 319 (0.31%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERCALCAEMIA			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERKALAEMIA			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOPHAGIA			
subjects affected / exposed	0 / 183 (0.00%)	1 / 319 (0.31%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	1 / 183 (0.55%)	0 / 319 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total	Cohort B1:pr, pe	

		Female naïve	
Total subjects affected by serious adverse events			
subjects affected / exposed	147 / 502 (29.28%)	5 / 26 (19.23%)	
number of deaths (all causes)	12	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BRONCHIAL CARCINOMA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CANCER PAIN			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLON CANCER			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO BONE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO SPINE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL CELL CARCINOMA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

SQUAMOUS CELL CARCINOMA OF THE TONGUE			
subjects affected / exposed	1 / 502 (0.20%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR PAIN			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
CIRCULATORY COLLAPSE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE CRISIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMPLICATION OF DEVICE INSERTION			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
FATIGUE			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	7 / 502 (1.39%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	3 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED HEALING			
subjects affected / exposed	3 / 502 (0.60%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	7 / 502 (1.39%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

PELVIC PAIN			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	12 / 502 (2.39%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	3 / 13	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERVENTILATION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	6 / 502 (1.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PNEUMONITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

PULMONARY EMBOLISM			
subjects affected / exposed	8 / 502 (1.59%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 8	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
PULMONARY FIBROSIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANIC ATTACK			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOMATIC SYMPTOM DISORDER			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
DEVICE LOOSENING			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	6 / 502 (1.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	4 / 502 (0.80%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (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 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 502 (0.20%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 502 (0.20%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ACCIDENT			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

ANKLE FRACTURE			
subjects affected / exposed	1 / 502 (0.20%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CERVICAL VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	3 / 502 (0.60%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCISIONAL HERNIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JAW FRACTURE			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 502 (0.20%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST-TRAUMATIC PAIN			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTOPERATIVE ADHESION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCEDURAL COMPLICATION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			
subjects affected / exposed	3 / 502 (0.60%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TIBIA FRACTURE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER LIMB FRACTURE			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	4 / 502 (0.80%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYARRHYTHMIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBRAL ISCHAEMIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			

subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MONOPLEGIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAESTHESIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL NERVE LESION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			

subjects affected / exposed	8 / 502 (1.59%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	20 / 23	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISSEMINATED INTRAVASCULAR COAGULATION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	3 / 502 (0.60%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
HYPERFIBRINOLYSIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	4 / 502 (0.80%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	3 / 502 (0.60%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			

subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN LOWER			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL HAEMORRHAGE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	4 / 502 (0.80%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	3 / 502 (0.60%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
INTESTINAL STRANGULATION			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	9 / 502 (1.79%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	2 / 11	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
VOMITING			
subjects affected / exposed	3 / 502 (0.60%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
BILE DUCT STENOSIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY COLIC			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG-INDUCED LIVER INJURY			

subjects affected / exposed	6 / 502 (1.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CIRRHOSIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOTOXICITY			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JAUNDICE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	6 / 502 (1.20%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	1 / 6	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
HAEMATURIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
KIDNEY CONGESTION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL DISORDER			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL IMPAIRMENT			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETERIC STENOSIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETEROLITHIASIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY INCONTINENCE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT OBSTRUCTION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
HYPERTHYROIDISM			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE LESION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
subjects affected / exposed	4 / 502 (0.80%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLANK PAIN			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUMBAR SPINAL STENOSIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MOBILITY DECREASED			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL CHEST PAIN			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOARTHRITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS OF JAW			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL PAIN			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABDOMINAL ABSCESS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS JAW			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATYPICAL PNEUMONIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS INFECTIVE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS ESCHERICHIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DIVERTICULITIS			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMPHYSEMATOUS CHOLECYSTITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	3 / 502 (0.60%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA INFECTION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE INFECTION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL INFECTION			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HELICOBACTER GASTRITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIOUS PLEURAL EFFUSION			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MASTITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	10 / 502 (1.99%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	3 / 10	0 / 0	
deaths causally related to treatment / all	1 / 3	0 / 0	
PROTEUS INFECTION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY SYNCYTIAL VIRUS INFECTION			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	3 / 502 (0.60%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	2 / 502 (0.40%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERCALCAEMIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOPHAGIA			

subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	1 / 502 (0.20%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort B:pr, pe, po Male or Female naïve+pre-tr.	Cohort A:po male or Female	Cohort B2:pr, pe, po Male or Female pre-tr.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	181 / 183 (98.91%)	315 / 319 (98.75%)	156 / 157 (99.36%)
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	30 / 183 (16.39%)	44 / 319 (13.79%)	19 / 157 (12.10%)
occurrences (all)	35	49	22
HYPERTENSION			
subjects affected / exposed	11 / 183 (6.01%)	36 / 319 (11.29%)	7 / 157 (4.46%)
occurrences (all)	13	38	9
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	74 / 183 (40.44%)	123 / 319 (38.56%)	59 / 157 (37.58%)
occurrences (all)	86	151	70
OEDEMA PERIPHERAL			
subjects affected / exposed	22 / 183 (12.02%)	35 / 319 (10.97%)	17 / 157 (10.83%)
occurrences (all)	31	37	24
PYREXIA			
subjects affected / exposed	14 / 183 (7.65%)	23 / 319 (7.21%)	10 / 157 (6.37%)
occurrences (all)	19	31	12
Immune system disorders			
SEASONAL ALLERGY			
subjects affected / exposed	6 / 183 (3.28%)	4 / 319 (1.25%)	3 / 157 (1.91%)
occurrences (all)	6	4	3
Reproductive system and breast			

disorders			
VULVOVAGINAL DRYNESS			
subjects affected / exposed	3 / 183 (1.64%)	4 / 319 (1.25%)	0 / 157 (0.00%)
occurrences (all)	3	5	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	22 / 183 (12.02%)	53 / 319 (16.61%)	16 / 157 (10.19%)
occurrences (all)	26	66	19
DYSPNOEA			
subjects affected / exposed	25 / 183 (13.66%)	49 / 319 (15.36%)	21 / 157 (13.38%)
occurrences (all)	26	58	22
OROPHARYNGEAL PAIN			
subjects affected / exposed	7 / 183 (3.83%)	11 / 319 (3.45%)	2 / 157 (1.27%)
occurrences (all)	9	12	2
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	8 / 183 (4.37%)	7 / 319 (2.19%)	6 / 157 (3.82%)
occurrences (all)	8	9	6
INSOMNIA			
subjects affected / exposed	26 / 183 (14.21%)	31 / 319 (9.72%)	22 / 157 (14.01%)
occurrences (all)	28	34	23
SLEEP DISORDER			
subjects affected / exposed	10 / 183 (5.46%)	13 / 319 (4.08%)	6 / 157 (3.82%)
occurrences (all)	10	15	6
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	36 / 183 (19.67%)	75 / 319 (23.51%)	30 / 157 (19.11%)
occurrences (all)	43	93	33
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	36 / 183 (19.67%)	66 / 319 (20.69%)	31 / 157 (19.75%)
occurrences (all)	44	82	36
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	1 / 183 (0.55%)	16 / 319 (5.02%)	1 / 157 (0.64%)
occurrences (all)	1	17	1
BLOOD CREATININE INCREASED			

subjects affected / exposed	12 / 183 (6.56%)	27 / 319 (8.46%)	10 / 157 (6.37%)
occurrences (all)	13	38	11
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	3 / 183 (1.64%)	17 / 319 (5.33%)	2 / 157 (1.27%)
occurrences (all)	4	22	3
BLOOD THYROID STIMULATING HORMONE INCREASED			
subjects affected / exposed	2 / 183 (1.09%)	0 / 319 (0.00%)	0 / 157 (0.00%)
occurrences (all)	2	0	0
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	14 / 183 (7.65%)	23 / 319 (7.21%)	13 / 157 (8.28%)
occurrences (all)	19	29	18
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	18 / 183 (9.84%)	33 / 319 (10.34%)	13 / 157 (8.28%)
occurrences (all)	20	38	15
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	25 / 183 (13.66%)	40 / 319 (12.54%)	23 / 157 (14.65%)
occurrences (all)	75	164	73
WEIGHT DECREASED			
subjects affected / exposed	9 / 183 (4.92%)	16 / 319 (5.02%)	9 / 157 (5.73%)
occurrences (all)	12	17	12
WEIGHT INCREASED			
subjects affected / exposed	4 / 183 (2.19%)	7 / 319 (2.19%)	2 / 157 (1.27%)
occurrences (all)	5	7	2
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	18 / 183 (9.84%)	27 / 319 (8.46%)	16 / 157 (10.19%)
occurrences (all)	21	56	19
Injury, poisoning and procedural complications			
ARTHROPOD BITE			
subjects affected / exposed	3 / 183 (1.64%)	3 / 319 (0.94%)	1 / 157 (0.64%)
occurrences (all)	3	3	1
ARTHROPOD STING			
subjects affected / exposed	2 / 183 (1.09%)	0 / 319 (0.00%)	0 / 157 (0.00%)
occurrences (all)	2	0	0

Nervous system disorders			
DIZZINESS			
subjects affected / exposed	12 / 183 (6.56%)	26 / 319 (8.15%)	8 / 157 (5.10%)
occurrences (all)	17	30	9
DYSGEUSIA			
subjects affected / exposed	11 / 183 (6.01%)	20 / 319 (6.27%)	7 / 157 (4.46%)
occurrences (all)	12	21	8
HEADACHE			
subjects affected / exposed	36 / 183 (19.67%)	56 / 319 (17.55%)	26 / 157 (16.56%)
occurrences (all)	55	90	35
HYPOAESTHESIA			
subjects affected / exposed	5 / 183 (2.73%)	3 / 319 (0.94%)	2 / 157 (1.27%)
occurrences (all)	5	3	2
POLYNEUROPATHY			
subjects affected / exposed	5 / 183 (2.73%)	16 / 319 (5.02%)	4 / 157 (2.55%)
occurrences (all)	5	17	4
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	36 / 183 (19.67%)	46 / 319 (14.42%)	29 / 157 (18.47%)
occurrences (all)	60	60	41
LEUKOPENIA			
subjects affected / exposed	39 / 183 (21.31%)	76 / 319 (23.82%)	31 / 157 (19.75%)
occurrences (all)	108	183	63
LYMPHOPENIA			
subjects affected / exposed	2 / 183 (1.09%)	7 / 319 (2.19%)	0 / 157 (0.00%)
occurrences (all)	13	14	0
NEUTROPENIA			
subjects affected / exposed	88 / 183 (48.09%)	162 / 319 (50.78%)	73 / 157 (46.50%)
occurrences (all)	326	558	231
THROMBOCYTOPENIA			
subjects affected / exposed	18 / 183 (9.84%)	26 / 319 (8.15%)	17 / 157 (10.83%)
occurrences (all)	23	46	21
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	17 / 183 (9.29%)	33 / 319 (10.34%)	13 / 157 (8.28%)
occurrences (all)	17	41	13
Eye disorders			

DRY EYE			
subjects affected / exposed	10 / 183 (5.46%)	23 / 319 (7.21%)	8 / 157 (5.10%)
occurrences (all)	11	24	9
LACRIMATION INCREASED			
subjects affected / exposed	11 / 183 (6.01%)	34 / 319 (10.66%)	9 / 157 (5.73%)
occurrences (all)	11	38	9
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	14 / 183 (7.65%)	15 / 319 (4.70%)	9 / 157 (5.73%)
occurrences (all)	17	21	10
ABDOMINAL PAIN UPPER			
subjects affected / exposed	13 / 183 (7.10%)	33 / 319 (10.34%)	10 / 157 (6.37%)
occurrences (all)	20	42	13
CONSTIPATION			
subjects affected / exposed	32 / 183 (17.49%)	62 / 319 (19.44%)	28 / 157 (17.83%)
occurrences (all)	43	71	39
DIARRHOEA			
subjects affected / exposed	40 / 183 (21.86%)	85 / 319 (26.65%)	32 / 157 (20.38%)
occurrences (all)	57	133	41
DRY MOUTH			
subjects affected / exposed	10 / 183 (5.46%)	28 / 319 (8.78%)	9 / 157 (5.73%)
occurrences (all)	10	30	9
DYSPEPSIA			
subjects affected / exposed	14 / 183 (7.65%)	25 / 319 (7.84%)	12 / 157 (7.64%)
occurrences (all)	14	28	12
NAUSEA			
subjects affected / exposed	77 / 183 (42.08%)	130 / 319 (40.75%)	68 / 157 (43.31%)
occurrences (all)	108	202	97
STOMATITIS			
subjects affected / exposed	27 / 183 (14.75%)	33 / 319 (10.34%)	23 / 157 (14.65%)
occurrences (all)	30	40	26
TOOTHACHE			
subjects affected / exposed	4 / 183 (2.19%)	9 / 319 (2.82%)	2 / 157 (1.27%)
occurrences (all)	4	10	2
VOMITING			

subjects affected / exposed	31 / 183 (16.94%)	66 / 319 (20.69%)	26 / 157 (16.56%)
occurrences (all)	63	93	53
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	57 / 183 (31.15%)	119 / 319 (37.30%)	52 / 157 (33.12%)
occurrences (all)	63	127	56
DRY SKIN			
subjects affected / exposed	15 / 183 (8.20%)	24 / 319 (7.52%)	12 / 157 (7.64%)
occurrences (all)	16	27	13
ERYTHEMA			
subjects affected / exposed	10 / 183 (5.46%)	9 / 319 (2.82%)	9 / 157 (5.73%)
occurrences (all)	10	9	9
PRURITUS			
subjects affected / exposed	18 / 183 (9.84%)	45 / 319 (14.11%)	15 / 157 (9.55%)
occurrences (all)	19	53	15
RASH			
subjects affected / exposed	19 / 183 (10.38%)	47 / 319 (14.73%)	17 / 157 (10.83%)
occurrences (all)	25	60	22
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	39 / 183 (21.31%)	57 / 319 (17.87%)	30 / 157 (19.11%)
occurrences (all)	47	76	35
BACK PAIN			
subjects affected / exposed	24 / 183 (13.11%)	37 / 319 (11.60%)	20 / 157 (12.74%)
occurrences (all)	29	42	23
BONE PAIN			
subjects affected / exposed	15 / 183 (8.20%)	35 / 319 (10.97%)	9 / 157 (5.73%)
occurrences (all)	18	42	9
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	6 / 183 (3.28%)	12 / 319 (3.76%)	4 / 157 (2.55%)
occurrences (all)	7	13	5
MUSCULOSKELETAL PAIN			
subjects affected / exposed	14 / 183 (7.65%)	21 / 319 (6.58%)	12 / 157 (7.64%)
occurrences (all)	15	27	12
MYALGIA			

subjects affected / exposed	6 / 183 (3.28%)	18 / 319 (5.64%)	6 / 157 (3.82%)
occurrences (all)	7	18	7
PAIN IN EXTREMITY			
subjects affected / exposed	23 / 183 (12.57%)	52 / 319 (16.30%)	20 / 157 (12.74%)
occurrences (all)	35	68	30
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	5 / 183 (2.73%)	19 / 319 (5.96%)	4 / 157 (2.55%)
occurrences (all)	6	25	5
CYSTITIS			
subjects affected / exposed	9 / 183 (4.92%)	21 / 319 (6.58%)	6 / 157 (3.82%)
occurrences (all)	10	25	7
GASTROINTESTINAL INFECTION			
subjects affected / exposed	3 / 183 (1.64%)	2 / 319 (0.63%)	1 / 157 (0.64%)
occurrences (all)	3	2	1
NASOPHARYNGITIS			
subjects affected / exposed	49 / 183 (26.78%)	94 / 319 (29.47%)	39 / 157 (24.84%)
occurrences (all)	74	131	56
URINARY TRACT INFECTION			
subjects affected / exposed	17 / 183 (9.29%)	31 / 319 (9.72%)	16 / 157 (10.19%)
occurrences (all)	23	45	21
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	19 / 183 (10.38%)	44 / 319 (13.79%)	18 / 157 (11.46%)
occurrences (all)	20	45	19
HYPERKALAEMIA			
subjects affected / exposed	4 / 183 (2.19%)	6 / 319 (1.88%)	2 / 157 (1.27%)
occurrences (all)	6	18	2
HYPOCALCAEMIA			
subjects affected / exposed	5 / 183 (2.73%)	8 / 319 (2.51%)	3 / 157 (1.91%)
occurrences (all)	5	10	3

Non-serious adverse events	Total	Cohort B1:pr, pe Female naïve	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	496 / 502 (98.80%)	25 / 26 (96.15%)	
Vascular disorders			

HOT FLUSH			
subjects affected / exposed	74 / 502 (14.74%)	11 / 26 (42.31%)	
occurrences (all)	84	13	
HYPERTENSION			
subjects affected / exposed	47 / 502 (9.36%)	4 / 26 (15.38%)	
occurrences (all)	51	4	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	197 / 502 (39.24%)	15 / 26 (57.69%)	
occurrences (all)	237	16	
OEDEMA PERIPHERAL			
subjects affected / exposed	57 / 502 (11.35%)	5 / 26 (19.23%)	
occurrences (all)	68	7	
PYREXIA			
subjects affected / exposed	37 / 502 (7.37%)	4 / 26 (15.38%)	
occurrences (all)	50	7	
Immune system disorders			
SEASONAL ALLERGY			
subjects affected / exposed	10 / 502 (1.99%)	3 / 26 (11.54%)	
occurrences (all)	10	3	
Reproductive system and breast disorders			
VULVOVAGINAL DRYNESS			
subjects affected / exposed	7 / 502 (1.39%)	3 / 26 (11.54%)	
occurrences (all)	8	3	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	75 / 502 (14.94%)	6 / 26 (23.08%)	
occurrences (all)	92	7	
DYSPNOEA			
subjects affected / exposed	74 / 502 (14.74%)	4 / 26 (15.38%)	
occurrences (all)	84	4	
OROPHARYNGEAL PAIN			
subjects affected / exposed	18 / 502 (3.59%)	5 / 26 (19.23%)	
occurrences (all)	21	7	
Psychiatric disorders			

DEPRESSION			
subjects affected / exposed	15 / 502 (2.99%)	2 / 26 (7.69%)	
occurrences (all)	17	2	
INSOMNIA			
subjects affected / exposed	57 / 502 (11.35%)	4 / 26 (15.38%)	
occurrences (all)	62	5	
SLEEP DISORDER			
subjects affected / exposed	23 / 502 (4.58%)	4 / 26 (15.38%)	
occurrences (all)	25	4	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	111 / 502 (22.11%)	6 / 26 (23.08%)	
occurrences (all)	136	10	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	102 / 502 (20.32%)	5 / 26 (19.23%)	
occurrences (all)	126	8	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	17 / 502 (3.39%)	0 / 26 (0.00%)	
occurrences (all)	18	0	
BLOOD CREATININE INCREASED			
subjects affected / exposed	39 / 502 (7.77%)	2 / 26 (7.69%)	
occurrences (all)	51	2	
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	20 / 502 (3.98%)	1 / 26 (3.85%)	
occurrences (all)	26	1	
BLOOD THYROID STIMULATING HORMONE INCREASED			
subjects affected / exposed	2 / 502 (0.40%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	37 / 502 (7.37%)	1 / 26 (3.85%)	
occurrences (all)	48	1	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			

subjects affected / exposed	51 / 502 (10.16%)	5 / 26 (19.23%)	
occurrences (all)	58	5	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	65 / 502 (12.95%)	2 / 26 (7.69%)	
occurrences (all)	239	2	
WEIGHT DECREASED			
subjects affected / exposed	25 / 502 (4.98%)	0 / 26 (0.00%)	
occurrences (all)	29	0	
WEIGHT INCREASED			
subjects affected / exposed	11 / 502 (2.19%)	2 / 26 (7.69%)	
occurrences (all)	12	3	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	45 / 502 (8.96%)	2 / 26 (7.69%)	
occurrences (all)	77	2	
Injury, poisoning and procedural complications			
ARTHROPOD BITE			
subjects affected / exposed	6 / 502 (1.20%)	2 / 26 (7.69%)	
occurrences (all)	6	2	
ARTHROPOD STING			
subjects affected / exposed	2 / 502 (0.40%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	38 / 502 (7.57%)	4 / 26 (15.38%)	
occurrences (all)	47	8	
DYSGEUSIA			
subjects affected / exposed	31 / 502 (6.18%)	4 / 26 (15.38%)	
occurrences (all)	33	4	
HEADACHE			
subjects affected / exposed	92 / 502 (18.33%)	10 / 26 (38.46%)	
occurrences (all)	145	20	
HYPOAESTHESIA			
subjects affected / exposed	8 / 502 (1.59%)	3 / 26 (11.54%)	
occurrences (all)	8	3	
POLYNEUROPATHY			

subjects affected / exposed	21 / 502 (4.18%)	1 / 26 (3.85%)	
occurrences (all)	22	1	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	82 / 502 (16.33%)	7 / 26 (26.92%)	
occurrences (all)	120	19	
LEUKOPENIA			
subjects affected / exposed	115 / 502 (22.91%)	8 / 26 (30.77%)	
occurrences (all)	291	45	
LYMPHOPENIA			
subjects affected / exposed	9 / 502 (1.79%)	2 / 26 (7.69%)	
occurrences (all)	27	13	
NEUTROPENIA			
subjects affected / exposed	250 / 502 (49.80%)	15 / 26 (57.69%)	
occurrences (all)	884	95	
THROMBOCYTOPENIA			
subjects affected / exposed	44 / 502 (8.76%)	1 / 26 (3.85%)	
occurrences (all)	69	2	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	50 / 502 (9.96%)	4 / 26 (15.38%)	
occurrences (all)	58	4	
Eye disorders			
DRY EYE			
subjects affected / exposed	33 / 502 (6.57%)	2 / 26 (7.69%)	
occurrences (all)	35	2	
LACRIMATION INCREASED			
subjects affected / exposed	45 / 502 (8.96%)	2 / 26 (7.69%)	
occurrences (all)	49	2	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	29 / 502 (5.78%)	5 / 26 (19.23%)	
occurrences (all)	38	7	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	46 / 502 (9.16%)	3 / 26 (11.54%)	
occurrences (all)	62	7	
CONSTIPATION			

subjects affected / exposed	94 / 502 (18.73%)	4 / 26 (15.38%)	
occurrences (all)	114	4	
DIARRHOEA			
subjects affected / exposed	125 / 502 (24.90%)	8 / 26 (30.77%)	
occurrences (all)	190	16	
DRY MOUTH			
subjects affected / exposed	38 / 502 (7.57%)	1 / 26 (3.85%)	
occurrences (all)	40	1	
DYSPEPSIA			
subjects affected / exposed	39 / 502 (7.77%)	2 / 26 (7.69%)	
occurrences (all)	42	2	
NAUSEA			
subjects affected / exposed	207 / 502 (41.24%)	9 / 26 (34.62%)	
occurrences (all)	310	11	
STOMATITIS			
subjects affected / exposed	60 / 502 (11.95%)	4 / 26 (15.38%)	
occurrences (all)	70	4	
TOOTHACHE			
subjects affected / exposed	13 / 502 (2.59%)	2 / 26 (7.69%)	
occurrences (all)	14	2	
VOMITING			
subjects affected / exposed	97 / 502 (19.32%)	5 / 26 (19.23%)	
occurrences (all)	156	10	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	176 / 502 (35.06%)	5 / 26 (19.23%)	
occurrences (all)	190	7	
DRY SKIN			
subjects affected / exposed	39 / 502 (7.77%)	3 / 26 (11.54%)	
occurrences (all)	43	3	
ERYTHEMA			
subjects affected / exposed	19 / 502 (3.78%)	1 / 26 (3.85%)	
occurrences (all)	19	1	
PRURITUS			
subjects affected / exposed	63 / 502 (12.55%)	3 / 26 (11.54%)	
occurrences (all)	72	4	

RASH			
subjects affected / exposed	66 / 502 (13.15%)	2 / 26 (7.69%)	
occurrences (all)	85	3	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	96 / 502 (19.12%)	9 / 26 (34.62%)	
occurrences (all)	123	12	
BACK PAIN			
subjects affected / exposed	61 / 502 (12.15%)	4 / 26 (15.38%)	
occurrences (all)	71	6	
BONE PAIN			
subjects affected / exposed	50 / 502 (9.96%)	6 / 26 (23.08%)	
occurrences (all)	60	9	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	18 / 502 (3.59%)	2 / 26 (7.69%)	
occurrences (all)	20	2	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	35 / 502 (6.97%)	2 / 26 (7.69%)	
occurrences (all)	42	3	
MYALGIA			
subjects affected / exposed	24 / 502 (4.78%)	0 / 26 (0.00%)	
occurrences (all)	25	0	
PAIN IN EXTREMITY			
subjects affected / exposed	75 / 502 (14.94%)	3 / 26 (11.54%)	
occurrences (all)	103	5	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	24 / 502 (4.78%)	1 / 26 (3.85%)	
occurrences (all)	31	1	
CYSTITIS			
subjects affected / exposed	30 / 502 (5.98%)	3 / 26 (11.54%)	
occurrences (all)	35	3	
GASTROINTESTINAL INFECTION			
subjects affected / exposed	5 / 502 (1.00%)	2 / 26 (7.69%)	
occurrences (all)	5	2	
NASOPHARYNGITIS			

subjects affected / exposed	143 / 502 (28.49%)	10 / 26 (38.46%)	
occurrences (all)	205	18	
URINARY TRACT INFECTION			
subjects affected / exposed	48 / 502 (9.56%)	1 / 26 (3.85%)	
occurrences (all)	68	2	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	63 / 502 (12.55%)	1 / 26 (3.85%)	
occurrences (all)	65	1	
HYPERKALAEMIA			
subjects affected / exposed	10 / 502 (1.99%)	2 / 26 (7.69%)	
occurrences (all)	24	4	
HYPOCALCAEMIA			
subjects affected / exposed	13 / 502 (2.59%)	2 / 26 (7.69%)	
occurrences (all)	15	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2016	The purpose of this amendment was to include feedback received from BfArM and ECs during the assessment of the initial application.
03 May 2017	This amendment was intended to update the existing information about ribociclib, to clarify specific aspects of the original protocol and to introduce the option for treatment beyond radiologic progression at the investigators discretion.
14 August 2017	This amendment was intended to correct mistakes in the protocol
05 May 2019	This amendment was intended to update the existing information about ribociclib, to clarify specific aspects of the original protocol and to introduce the option for treatment beyond radiologic progression at the investigators discretion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported